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A Practical Journal on Psychiatry and Neurology

MARCH

1958

(CONTENTS ON PAGE 92)

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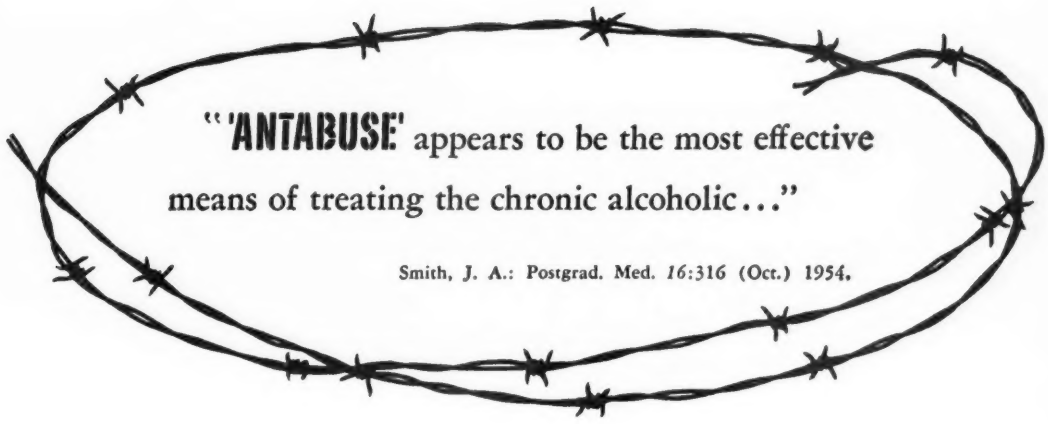

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DISEASES *of the* Nervous System

Contents

FACTORS INFLUENCING ACADEMIC ACHIEVEMENT 97
F. J. Ryan and W. G. Scanlon

EFFECT OF NIACIN ON THE ELECTROENCEPHALOGRAM OF PSYCHOSIS WITH CEREBRAL ARTERIOSCLEROSIS 100
P. O. O'Reilly and R. P. Keogh

RECOVERY FROM INSULIN COMA AND HEMATOENCEPHALIC EXCHANGE 104
Williamina A. Himwich and JoAnn C. Petersen

VARIOUS ETIOLOGIES OF THE SCHIZOPHRENIC SYNDROME 108
David A. Freedman

EXPERIMENTAL STUDIES OF THE ELECTROSHOCK PROCESS 113
Max Fink, Robert L. Kahn and Martin A. Green

PROCHLORPERAZINE IN HOSPITALIZED AND PRIVATE PSYCHIATRIC PATIENTS 118
Frank Wilcox

ADVANTAGES OF COMBINED RITALIN AND SERPASIL THERAPY IN CHRONIC PSYCHOSES 122
John C. Saunders and Nathan S. Kline

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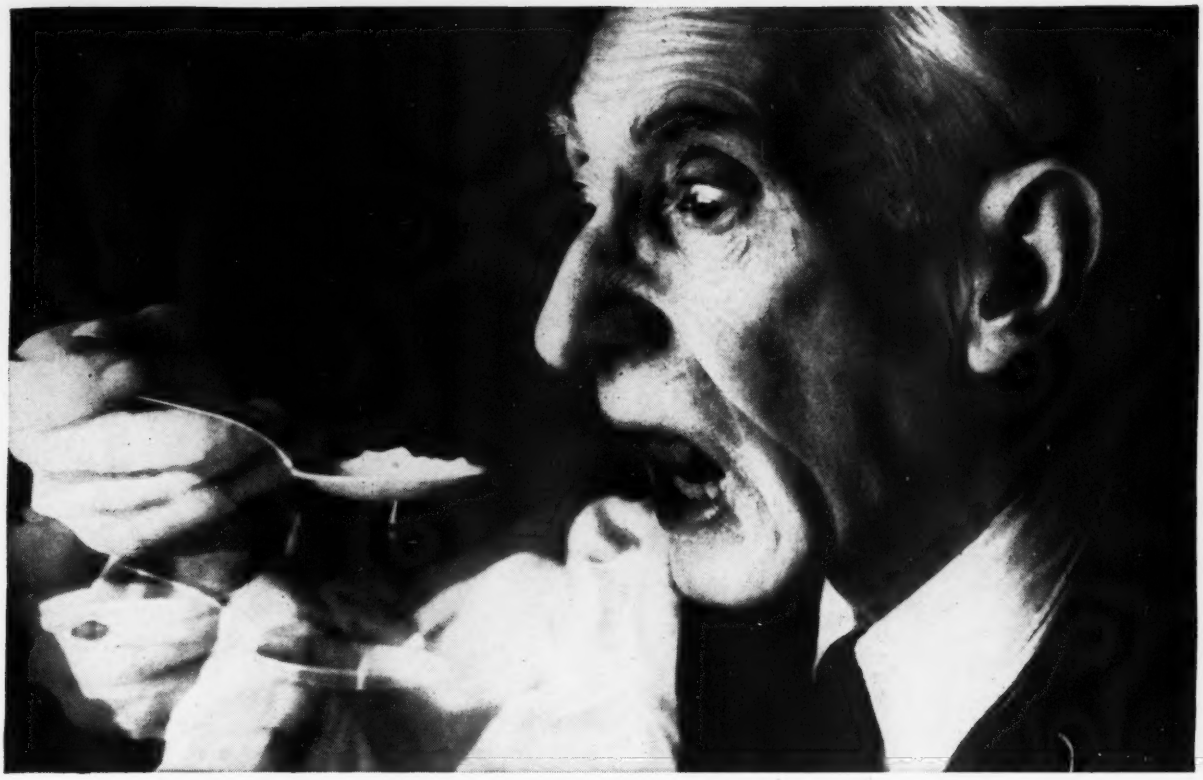

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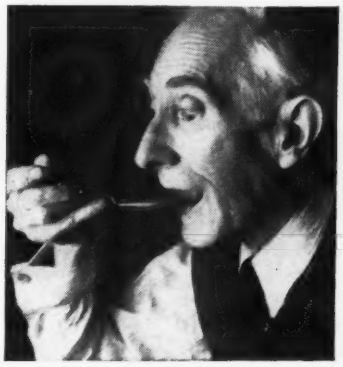

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DISEASES *of the* Nervous System

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Factors Influencing Academic Achievement

Some Considerations in a Research Approach to the Problems of Mental Health and Academic Achievement

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F. J. RYAN, PH.D., and W. G. SCANLON, M.D.

The college or school psychiatrist, the psychologist, and the educator are constantly concerned with the problem of academic success and failure. Also, on occasion, this problem may be of concern to any psychotherapist who has young patients.

Often, upon the completion of what seems to be successful psychiatric treatment, the physician is puzzled to find that there is little or no improvement in the student's grade record. In some cases there may even be a drop in achievement. Thus, the psychiatrist, the parents and the educator get their first hint that the relationship between mental health and academic achievement may be quite complex, a hint that is confirmed by a study of the literature.

The realization some years ago that the aptitude testing movement had reached a point of diminishing returns in its ability to account for academic achievement, touched off an extensive search for the "non-intellectual" factors that would increase prediction and understanding of performance in the classroom. A wide range of variables was explored. One of the most promising approaches appeared to be mental health and personal adjustment, probably because a simple and obvious hypothesis offered itself: given a constant intelligence, the student's grade record should be a direct function of his mental health.

The designs of nearly all such studies involved either two contrasted groups (comparing the academic performance of students with good mental health with the performance of those with poor mental health) or correlational techniques (relating mental health to achievement), thus indicating a search for linear relationships. For the most part the criteria of mental health were the adjustment of psychoneurotic inventories. Each known instrument was used at least several times, and new ones were devised. These early studies have been summarized by many authors.[12,13,22,23,25] In general the measured relationship between achievement and indices of mental health tended to be small, non-significant and often negative.

The effort to relate academic achievement to mental health and its various measured dimensions still goes on. Though more recently developed and more sophisticated instruments of appraisal are employed, the results seem approximately the same. For example, Clark[5] found that "Poor grades are not related to any specific syndrome measured by the MMPI . . ." Similar results with the Minnesota Multiphasic Personality Inventory have been obtained by other investigators.[1,6] However, the scales of the MMPI seem to have some predictive value for achievement when used on an empirical basis.[10,11]

The Rorschach Test, because it has such wide clinical acceptance, has been used extensively to explore the relationship between adjustment and academic achievent. An analysis of investigations with this projective method[19] shows that Rorschach adjustment scores usually do not correlate with achievement. One study,[16] carried out in an atypical school, produced such a correlation, but this finding was not reproduced elsewhere.[7]

This is the first report on a continuing research project dealing with academic achievement that was originated by the Silver Hill Foundation. This study is supported by the Foundation and is being carried out in conjunction with the New Canaan Public Schools. Doctor Ryan is the principal investigator.

It would seem fair to summarize most of this research work as follows: Empirical methods of scoring can be constructed for many tests which tend to correlate to some degree with academic achievement. However, measures of adjustment derived from such instruments do not tend to yield correlations with achievement.

Even if the validity of the techniques used in these investigations is challenged, the conclusions are supported by other evidence. As far back as 1936, Raphael[17] noted that patients seen at a college mental hygiene clinic performed as well scholastically as did nonpatients in the student group. At the Division of Psychiatry and Mental Hygiene of Yale University it was found that the higher proportion of psychiatric patients among underachievers was only barely significant, even though many patients were referred by the dean's office because of academic difficulties. In an investigation at the same clinic, Davie[5] found all shades of scholastic achievement well represented in the patient load.

Further, the recent publications of Harrison[14] and Darling[4] indicate that both prepsychotic and post-psychotic personalities often can function well academically. Among the faculty at a suburban high school, a team of investigators[2] (p. 201) found: "There would . . . appear to be a negative correlation between years of education and adjustment. . . ."

In view of the evidence available thus far, should we abandon the area and accept the "finding" that mental health has nothing to do with achievement? Of course not! Acceptance of the null hypothesis does not square with common sense. Psychiatrists take it as a working certainty that emotional factors either predominate or play a part in all behavior. It would be a strange incongruity if one great area of interaction, school learning, were to be an exception. Instead, we can be virtually positive that emotional factors do, and perhaps vitally at times, affect academic achievement. The research task becomes that of specifying how. The literature only serves to warn that the undertaking is not a simple one. A realistic research approach will involve the recognition of many considerations, important among which are:

1. We must be prepared to relinquish the assumption that there is a linear relationship between school learning and mental health. The work of Stagner,[22] supplied a clue that has been largely overlooked or ignored. He found the correlation between grades and aptitude to be lower among students with poor measured adjustment. Among patients seen at the Division of Student Mental Hygiene at Yale, Rust[18] found the correlation between Scholastic Aptitude Tests scores and average grades to be only .19. Serene[20] reports that psychotherapy tends to increase such a lowered correlation among patient groups. The finding is further supported by the work of Hoyt.[15] The important point seems to be that the presence of emotional upset may introduce a new variance—i.e., poor personal adjustment tends to produce *both* under- and over-achievement. In other words, emotional problems may drive one student away from his work and another toward it.

2. A thorough examination of emotional factors and academic achievement can scarcely ignore the human cost that achievement may involve. Two students with similar aptitudes and achievements could well be operating on quite different bases. One may go about his work with great zest, finding pleasure and fascination in the world of words, ideas, books, numbers, maps, etc. The other, with comparable measured achievement, may work in a painful, guilt-ridden, compulsive manner. Beck[3] has cited cases to suggest that outstanding academic achievement can, in some instances, represent a lopsided and costly adjustment made at the expense of other and possibly more important adjustments.

3. We must be wary of the assumption that there "is something wrong" with the boy who makes very little academic effort. From the professional educator's viewpoint there "is something wrong." However appropriate this position may be, it stems from a limited perspective. Though excellence in school work is commendable, poor academic work is truly normal behavior in many instances.

4. Most research efforts have defined achievement on the basis of disparity between measured academic aptitude scores

and grade records. In this way the investigator presumes he has "equated for intelligence"—i.e., obtained experimental groups of equal intelligence. This procedure may be useful and difficult to improve upon in the present state of our knowledge. There can be no quarrel with the practical value of such tests, but research success in the area under consideration may depend upon viewing these instruments in a different and probably proper perspective. It must be remembered that these tests are basically work samples taken from the world of words and numbers; consequently, they do not directly measure the potential efficiency of the central nervous system. The student response to these tests may be affected by the same emotional factors that raise or lower academic performance.

5. The literature abounds in the case histories of failures and non-achievers. Patients often come to the psychiatrist with both an emotional problem and a poor academic record. If controls are lacking, inferences are difficult to draw. The "conclusions" from such studies on methodological grounds alone must be treated as nothing more than leads for further research.

Somewhat more persuasive than reports of individual cases are those studies[9,21] which present statistical demonstrations indicating that guidance can increase the grades of underachievers. However, in view of the finding that emotional problems tend to reduce the correlation between aptitude and achievement, it can be expected that therapy also may lower the grades of overachievers.

6. There is evidence[14] that studies of different types of psychiatric illness may be useful for research in achievement, yet it is clear that the psychiatrist's contribution to research in this field must go far beyond the use of diagnostic categories and their correlation with achievement. Studies of samples of psychiatric entities would have no application to samples of normal persons. Also, the exclusive use of such clinical labels would obscure behavior that might better be specified in descriptive terms.

The present limitations in our ability to specify the factors that affect academic learning are startling. Most research efforts in this vital area have been tantalizingly fruitless (for an evaluation of some 1000 such efforts see 24). Probably through an increased knowledge of the parts played in it by emotional factors, education can be made substantially more effective. Obviously, therefore, significant research contributions must be forthcoming from psychiatry if the part by emotions in the learning processes is to be properly evaluated. The present paper draws attention to some important consideration for future study that are suggested by past research experience. These and other related problems will be considered in subsequent publications.

Summary

This is the first of a series of reports on factors influencing academic achievement. A review of the psychological and psychiatric literature dealing with the subject indicates marked limitations in our ability to specify the emotional factors that influence the process of learning. Past investigations suggest that future studies must consider hypotheses other than those based on simple and direct relationship between mental health and academic achievement and be prepared to study and understand the more intimate relationships between emotions and learning.

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Effect of Niacin on the Electroencephalogram of Psychosis with Cerebral Arteriosclerosis

P. O. O'REILLY, M.B., B.CH., and R. P. KEOGH, R.T.

Introduction

Investigations have been carried out into the use of nicotinic acid as a therapeutic agent and their results reported.[10,14,16] In the field of psychosis with cerebral arteriosclerosis various authors[5,12,13] have described the effiicacy of small doses of nicotinic acid on the mental status of patients. Chittick et al.[2] in 1941 saw improvement in the physical condition of the elderly patient but did not observe concurrent psychological changes when the drug was administered for two to three weeks. A number of studies have reported that nicotinic acid given orally or intravenously to normal volunteers produced a slight shift in EEG frequency to the fast side: in epileptics the drug decreases considerably bilateral diffuse, paroxysmal abnormalities (except in true idiopathetic epilepsy) but has very little influence on the focus itself. Serra and Scoppa[17] stated that following the intravenous injection of nicotinic acid (45-65 mg. of the drug) there was a constant increase in the amplitude of the alpha waves especially in the parieto-occipital and central regions. In some instances there were also some paroxysmal discharges of theta and alpha waves in the parieto-occipital and temporal regions. On the basis of these observations the authors believe that the drug produces some metabolic modifications. Daneman, Chornesky and Haycox report the investigation of nicotinic acid in the treatment of cases of cerebral arteriosclerosis with psychosis using the EEG as one measure of evaluation. They state that changes in the EEG median for the worse occurred on niacin. These changes represented a definite worsening of the EEG frequency, lower rates being observed. They state that these EEG changes suggest that

From Saskatchewan Hospital, North Battleford, Canada.

nicotinic acid interfered with brain physiology as measured by the EEG causing a slowing to more pathological frequencies than were seen prior to the therapeutic trial. A reversion toward more normal Alpha frequency occurred when treatment was discontinued.

The purpose of this paper is to report the results of a pilot study of the effect of niacin on the EEG of individuals suffering from psychosis with cerebral arteriosclerosis.

Method

Nine male patients were chosen at random from cases of psychosis with cerebral arteriosclerosis. Diagnosis was based on the presence of a chronic syndrome, characterized by memory loss, periodic confusion, emotional lability and disorientation. History of a cerebral accident, headaches, dizziness and the presence of peripheral arteriosclerosis, arteriosclerotic retinopathy and arteriosclerotic heart disease were taken into account. Criteria for onset of illness were (a) memory changes, (b) history of cerebral accident, (c) onset of periods of confusion. The patients ranged in ages from 56 to 82 years, averaging 69.7 years of age. It was found that the patients varied in the duration of illness from one month to fifteen years.

EEG recordings were taken with an 8 channel apparatus. Each recording was made for 60 continuous minutes. The technique was the same for all patients. Unipolar and bipolar leads were used with 16

TABLE I

		Before Niacin	On Niacin	
No.	Age	1st EEG	2nd EEG	3rd EEG
1	61	Low voltage 20-30 uv. Predominantly fast 15 c/s in all areas.	No significant change.	Improvement only in the occipital areas rhythm to 11 per second.
2	63	Low voltage 20-30 uv. Dominantly fast 15 c/s with scattered slow 6-7 of increased voltage.	This recording shows an increased amount of the slow wave activity.	Improved the slow wave activity decreased to that noted in 1st EEG.
3	76	Low voltage 20-30 uv. Random slow wave activity 6 c/s in all areas at intervals with increased voltage.	No significant change.	No significant change.
4	56	Low voltage 20-30 uv. with random slow 5-6 c/s in all areas with some fast 15 c/s activity intermixed in recording.	No significant change.	No significant change.
5	75	Low voltage 20-30 uv. Dominant fast 15 c/s activity with scattered slow wave 6-7 c/s activity of increased voltage.	No significant change.	No significant change.
6	82	Low voltage 20-30 uv. with random slow 6-7 c/s in all areas appearing episodically with increased voltage.	No significant change.	No significant change.
7	78	Low voltage 20-30 uv. with a dominant fast 15 per second rhythm in all areas.	No significant change.	No significant change.
8	80	Moderate voltage 50 uv. with a dominant 11 per second rhythm and scatter-fast activity 15 c/s.	No significant change.	No significant change.
9	67	Moderate voltage 40-50 uv. with marked slow 5 per sec. activity with increased voltage in all areas.	The slow 5 per second activity is not evident in this EEG. There is a dominant 10 per sec. rhythm with isolated slow 7 per second activity.	No significant change from patient's 2nd EEG.

electrodes applied to the scalp using collodion. No sedation was administered. Each patient had a recording before starting niacin and the recording was repeated at the end of the first and second month on niacin.

Following the first recording the patients were placed on niacin one gram three times daily for three months.

Results

Examination of the above data shows the following results:

(1) Three patients showed EEG's within normal limits and continued while the patients were on nicotinic acid for two months without showing any significant change in rhythm.

(2) Six patients showed abnormal EEG's before niacin. Three patients showed no significant change during the two month trial period. One patient, after the end of the first month on niacin showed marked increase in the slow wave activity and at the end of the second month the slow activity was not so marked and had reverted to that seen in the pre-nicotinic acid EEG. One patient showed improvement only in the occipital areas, the rhythm becoming 11 per second. One patient, who on his pre-niacin EEG showed marked slow 5/cs activity showed marked improvement on niacin. His recordings on niacin showed a normal 10 per second rhythm in all areas with a few isolated slow seven per second activity of increased voltage.

Discussion

In comparing our data with results reported by others,[3] we find certain differences. Daneman[3] conducted his investigations on six patients receiving niacin with one repeat recording. He found a worsening of the EEG frequency and suggests that niacin interfered with brain physiology as measured by the EEG causing slowing to more pathological frequencies. The present studies indicate that niacin had no worsening effect as assessed by the EEG, but rather indicates that it effectuates a more normalizing pattern. In case number two, where a worsening occurred in the first month, continued medication led to a reversal to the pre-niacin recording. In case number nine, niacin produced a marked change leading to normalization over all areas of the head. On the basis of our studies it does appear that niacin may be useful in the treatment of cerebral arteriosclerosis with psychosis and if niacin has an effect on brain physiology it results in a recording indicating improvement. The difference in the findings between Daneman's data and ours is probably due to two factors:

(1) Daneman's dosage of niacin was 250 mgms. daily as opposed to 3 grams a day.

(2) Daneman's treatment period was one month as compared to a two-month trial period.

The action of niacin is not too clear. In the tissues nicotinic acid is built up into two complex co-enzymes, co-operating with dehydrogenases, i.e., co-enzyme I and co-enzyme II and they play an important role in hydrogen transport in the intermediary metabolism of the cell. These co-enzymes are links in the chain from metabolite to final oxidation by cytochrome oxidase. Studies of the intracranial circulation during nicotinic acid administration were made.[1] It was found that the lumbar outflow of spinal fluid increase suggesting that nicotinic acid would dilate the intracranial vessels. Scheinberg[16] however, in his experimentation reports that nicotinic acid in flushing doses does not produce cerebral vasodilation and that this drug has no place in the treatment of cerebral vascular diseases unless it possesses some therapeutic action aside from its effect on cerebral vessels.

Mechanism of Action

1. Lehman[11] feels nicotinic acid produces its effect by a mass action effect causing a shift in the balance of the co-enzyme system and producing a new compensatory mechanism.

2. Hoffer, Osmond, Callbeck and Kahan[10] postulate that nicotinic acid may restore inhibited diphosphopyridine nucleotide—triphosphopyridine nucleotide function.

Fazekas, Alman and Bessman[4] found cerebral oxygen consumption to be lower in the aged probably as a result of a certain universal degree of arteriosclerosis. Furthermore patients with clinical arteriosclerosis showed slightly lower oxygen consumption but this decrease was independent of the degree of involvement. They state that their

data suggests that decreased cerebral enzyme activity and/or impaired oxygen availability may contribute to the changes of function in the central nervous system function so frequently encountered in the aged. These findings have led Scheinberg and others[16] to postulate that this condition may be a failure of an enzyme or enzyme system.

Such failures of enzymic activity which have been found in other organic conditions such as general paresis bringing about respiratory difficulties in the brain tissue in all probability lead to the slowing and other abnormalities seen in the electroencephalogram. In general paresis Hadidian and Hoagland[6,7,8,9] found "reduction of available cytochrome oxidase" and as niacin is a co-enzyme in cellular metabolism involving cytochrome oxidase it is therefore likely that the enzymic action of niacin is responsible for the changes found in our data. The best results were obtained in one case (No. 9) of recent onset of psychosis (one month) which suggests that if niacin is given before irreversible changes occur it can produce normalization of brain pattern.

Summary

Nine patients with a diagnosis of cerebral arteriosclerosis with psychosis were placed on niacin 1 gram T.I.D., for a three-month period. Before starting niacin, an EEG recording was made and the recording was repeated at the end of the first and second month on niacin. Three patients had initial and subsequent recordings within normal limits. Six patients had abnormal initial EEG's. Four of these showed no significant change on niacin. Two patients showed improvement of the abnormal EEG's on niacin. A brief discussion on the results and possible action of niacin is presented.

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Recovery from Insulin Coma and Hematoencephalic Exchange

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The ability of the brain to metabolize glutamic acid either *in vitro* or under conditions of stress in which glucose is not available in sufficient quantities to maintain metabolism is well documented.[1,2,3,4] Both Mayer-Gross and Walker[5] and Weil-Malherbe[6] have succeeded in restoring patients in insulin hypoglycemia to environmental contact with glutamic acid. Petersen, Stripe and Himwich[7] have shown that glutamate but not glycine will protect rabbits from death due to hypoglycemia even though glycine is the more potent hyperglycemic agent in the normal rabbit. In the normal adult rabbit and adult rat a high level of blood glutamate does not affect the brain level of this amino acid.[8,9] These facts are usually taken to mean that in the adult glutamic acid penetrates the so-called blood-brain barrier very slowly. The experiments reported here were undertaken to determine if the entrance of glutamic acid into the brain could be influenced by deep insulin hypoglycemia and if such glutamic acid could be used by the brain to maintain the electrical activity of the cortex.

Method

All rabbits used for insulin hypoglycemia were starved at least 24 hours. At approximately 5 P.M. on the day before the experiment they received 8-12 units of protamine zinc insulin, the dose depending upon the weight of the animal. Every hour during the experimental day they received 40 units of regular insulin intramuscularly. The best response was obtained from animals who were convulsing at 8 A.M. on the day of the experiment. Such animals were injected with sufficient nembutal to control the convulsions, were restrained, and given artificial respiration. Two electrodes were implanted through the skull, one on the right motor cortex, the other on the left limbic cortex. A heart electrode was also used as an aid in following the cardiovascular changes. Throughout the day the animals were protected carefully against anoxia, against cold and against the muscular consequences of convulsions. In the hypoglycemic control animals the experiment was continued until the heart began to fail as evidenced by dysrhythmia and marked slowing. Such changes usually occurred between 3 and 4 o'clock in the afternoon after approximately 8-9 hours of deep hypoglycemia. The uniform procedure for removing the brain described by Himwich and Sullivan[4] and by Sullivan and Strong[8] was followed. Caudate nucleus samples included the head of the caudate and the adjacent frontal cortex; hemisphere samples refer to the remainder of the hemisphere with its underlying structures caudad through the superior colliculi. The samples were frozen immediately in dry ice and acetone and kept frozen until analyzed.

Normal control animals were treated in exactly the same fashion except they were neither starved nor was insulin administered. The rabbits received just sufficient barbiturate to keep them quiet when restrained. Artificial respiration was kept at a minimum to avoid alkalosis and concomitant spiking in the electroencephalogram.

The animals given glucose or glutamate were rendered hypoglycemic by the standard procedure given above. After the electroencephalogram had been practically flat for 2-3 hours, treatment was instituted for a period of 2 hours. Sodium glutamate at pH 7.0 was given to two groups of hypoglycemic rabbits. One group received subcutaneously 2 grams of L-glutamic acid per kilogram of body weight. The metabolic effects of such a dose in the normal and in the "mildly hypoglycemic" rabbit have been described by Petersen, Stripe and Himwich.[7] This dose raises blood glutamate 300-400 times. A second group of animals received

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the same solution of sodium glutamate diluted 1-5 with water as an intravenous drip over a period of 2 hours. Such animals received about 3 grams of L-glutamic acid per kilogram. Brains from both groups of animals were sampled as described above.

In order to study the effects of glucose, a third group of hypoglycemic animals were given 10% glucose in saline as an intravenous drip for 2 hours before the brains were removed. In this way the animals received approximately 20 grams of glucose.

Blood sugars were not determined on any of the animals reported in this paper. However, similarly treated animals reported by Himwich and Sullivan[4] and unpublished data from animals in the laboratory showed that terminal blood sugar values are below 15 milligrams per cent as determined by the Nelson[10] modification of the Somogyi method. Glutamic acid in brain was measured by the method of Prescott and Waelsch[11] as modified by Himwich and Petersen;[12] the glutamine by the method of Bessman and his colleagues.[13]

Results

The data from the control animals suggest that the caudate nucleus samples are richer in free glutamic acid and in glutamine than are the hemisphere samples (Table I). This fact is not surprising since the former samples contain a much higher proportion of cells than do the latter. Other data have shown that in rabbits the concentration of free glutamic acid is greater in areas rich in cell bodies.[14] It is of interest that α-ketoglutarate is about 6-7 times higher in these areas than in the hemispheres.[14] During deep insulin hypoglycemia approximately one-half of the free glutamic acid and a slightly larger percentage of glutamine disappear (Tables I and II).

When glutamic acid is given, the free glutamic acid of the brain is restored. For both routes the values are within the normal range, although they tend to be slightly lower for those animals receiving the amino acid intravenously. For glutamine the recovery is not as marked. If we consider the sum of the glutamic acid and glutamine, using figures from Tables I and II, the recovery is more complete in the caudate nucleus samples than in the hemisphere samples.

The administration of glucose had about the same effect upon the brain glutamic acid and glutamine as did that of glutamate (Tables I and II).

TABLE I

Free Glutamic Acid (mg %) in Brain Parts

	Hemisphere Samples				Caudate Nucl. Samples			
	Right		Left		Right		Left	
CONTROL:								
	(7)*	97.3	(7)	100.1	(7)	116.3	(7)	124.4
HYPOGLYCEMIC:								
	(10)	59.5	(10)	54.9	(9)	64.0	(9)	61.8
HYPOGLYCEMIC & GLUCOSE:								
SubQ	(6)	100.3	(6)	101.8	(6)	128.0	(6)	126.7
Drip	(5)	84.8	(5)	89.4	(3)	127.7	(3)	102.3
HYPOGLYCEMIC & GLUCOSE:								
	(5)	93.2	(5)	84.6	(4)	134.2	(5)	87.2

*No. animals used.

TABLE II

Glutamine (mg %) in Brain Parts

	Hemisphere Samples				Caudate Nucl. Samples			
	Right		Left		Right		Left	
CONTROL:								
	(7)*	46.7	(7)	44.3	(7)	61.1	(7)	69.1
HYPOGLYCEMIC:								
	(9)	19.4	(9)	17.4	(10)	26.2	(9)	39.2
HYPOGLYCEMIC & GLUTAMATE:								
SubQ	(5)	28.8	(5)	27.4	(6)	39.7	(5)	48.0
Drip	(4)	22.2	(4)	20.2	(2)	28.5	(3)	84.0
HYPOGLYCEMIC & GLUTAMATE:								
	(5)	23.8	(5)	27.4	(4)	49.5	(5)	63.8

*No. animals used.

The cortical electroencephalograms for motor and limbic areas are shown in Figure 1 as they appeared at 3:00 P.M. or close to the end of the experimental day. The control record is considered normal for a rabbit lightly anesthetized with nembutal. The record from the hypoglycemic animal is flat and had been without activity for three to four hours. The intravenous drips of glucose or glutamate were started at 1:00 P.M. The pattern for the animal receiving glucose has returned to the normal one for a rabbit while that for the animal receiving glutamate has been scarcely affected.

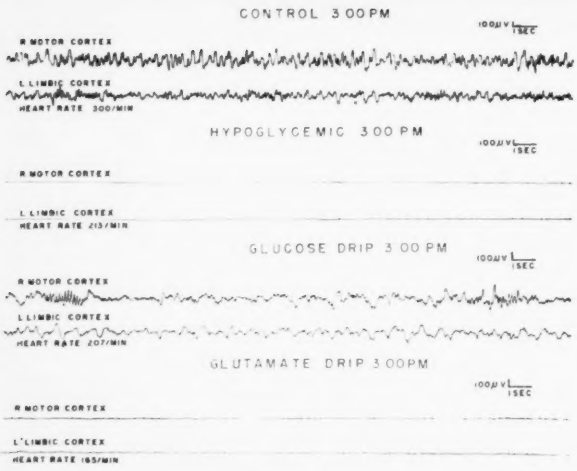

Figure 1. Cortical EEG's of control animals, hypoglycemic animals and hypoglycemic animals treated with glutamate and with glucose.

Discussion

These observations confirm and extend those of Dawson[1] and others[2,4] that free glutamic acid disappears during insulin hypoglycemia. They yield no data, however, on what has actually happened to the amino acid. If we conclude that it is contributing to the energy needs of the brain, we may assume that one pathway would be deamination and entrance into the citric acid cycle as α-keto-glutaric acid. The amino acid might, on the other hand, be decarboxylated to form amino butyric acid or lose a CH_2-group to become aspartic acid. Cravioto et al.[2] have shown some increase in aspartic acid during insulin hypoglycemia. Actually, the simultaneous determination of at least six metabolites would be necessary in order to trace completely the path by which the acid disappears in studies such as this.

If glutamic acid is burned by entering the citric acid cycle as α-keto-glutarate, its metabolism would probably proceed more rapidly when all components of the cycle are present in optimal amounts. The metabolism of glucose under normal circumstances undoubtedly primes the cycle with two carbon fragments at close to the optimal rate. At this rate additional amounts of α-keto-glutarate could be absorbed easily. However, when glucose is depleted as in hypoglycemia the cycle would have to depend upon two carbon fragments from other sources. While these would undoubtedly be available, it is doubtful if they would be present in sufficient amounts to activate the cycle at the same rate as do fragments from glucose. If they could, glucose would not be necessary. Under such conditions the accumulation of a single member of the cycle might even tend to slow down the transfer of energy. It would seem probable in any case that α-keto-glutarate would not serve as a significant source of energy in hypoglycemia. Even if we assume that the glutamic acid is contributing to the energy requirements of the brain it is still not capable of maintaining the electrical activity of the cortex, since the brain waves have disappeared even though approximately 50% of the glutamic acid is still present.

When the blood level of the glutamic acid is raised 300-400 times in profoundly hypoglycemic animals, the amino acid enters the brain and restores the brain level to normal. These data suggest that in deep insulin hypoglycemia the mechanism which prevents the entrance of glutamate from the blood is relaxed and the amino acid enters the brain freely. The controlling factor which normally keeps glutamate out may be no more than the presence of a given level of glutamic acid in the cells. In insulin hypoglycemia, the reduction in quantity of free glutamic acid would then permit its entrance from the blood. It might be argued that, in the normal adult animal, glutamic acid penetrates freely but is maintained at a given level by the tissue either through incorporating the entering amino acid into protein or by metabolizing it. Such a homeostatic mechanism would not function unless the content of free glutamic acid in the cells was at its normal level. We have no data nor do we know of any in the literature which provide an answer to these questions.

Animals in deep insulin hypoglycemia show a marked loss of potassium and an increase of sodium in the brain,[4] similar to that reported by Yannet[15] and by Geiger et al.[16] The cats studied by Yannet showed also marked neurological defects. From these data it might be assumed that when glutamic acid is raised in the blood during insulin hypoglycemia it floods the brain because of changes, either reversible or irreversible, in brain tissue and hence a loss of the regulatory function of the blood-brain

barrier. The recovery of cortical electroencephalogram of the animals given glucose, however, argues against this explanation. It is important that although glutamic acid returns to the normal adult level in the brain, in animals subjected to deep insulin hypoglycemia and treated with glutamate, the electroencephalogram is not restored. Such a failure of glutamic acid and of various other metabolites to maintain normal electrical activity of the cortex has been described by Maddock et al.[17] in eviscerated hypoglycemic animals. Our data on intact animals confirm their work.

It is not surprising that our animal experiments do not agree with the clinical reports that patients may be aroused from insulin hypoglycemia with glutamic acid. Such patients are not subjected to as strenuous a depletion of liver glycogen and of endocrine reserves as were our rabbits who were under intensive insulin treatment starting the day before the experiment. In the normal rabbit the hyperglycemic response to glutamate appears to be endocrine in nature. It seems likely that patients would have both the endocrine and glycogen reserves to respond to the amino acid just as do "mildly hypoglycemic" rabbits which readily recover after the administration of glutamate. The chief differences between the experiments reported in this paper and the clinical studies reported by Mayer-Gross and Walker[5] and by Weil-Malherbe[6] were the depth and duration of the hypoglycemia.

The administration of glucose in the absence of glutamate not only permits the electrical activity of the brain to return to normal but also restores the free glutamic acid level in the brain. We assume that the glutamic acid has been formed from the administered glucose. Such a metabolic change has been demonstrated *in vitro* by Beloff-Chain et al.[18] and by Winzler and his colleagues.[19] It is interesting that the brain even when in need of glucose diverts part of that foodstuff to the restoration of the normal level of glutamic acid.

Summary

In deep insulin hypoglycemia rabbit brain loses approximately fifty per cent of its normal content of free glutamic acid. Glutamic acid administered either intravenously or subcutaneously will restore the level of free glutamic acid but the cortical electroencephalogram does not return to normal. Glucose alone given intravenously increases the free glutamic acid in the brain and the normal pattern of the cortical electroencephalogram returns. From this we draw the following working assumptions; 1) that the free glutamic acid used by the brain during deep insulin hypoglycemia does not yield sufficient energy to maintain the cortical electroencephalogram; 2) administered glutamic acid enters the brain more freely in the animal subjected to deep insulin hypoglycemia than in the normal rabbit but does not influence significantly the electrical activity of the cortex; 3) treatment with glucose restores the glutamic acid level and the electrical activity.

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Various Etiologies of the Schizophrenic Syndrome

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Precise definition of the etiology of a disease is never an easy matter. Even in the relatively obvious instance of bacterial infection, isolation and identification of a pathogenic organism does not provide the complete explanation for the presence of an associated syndrome. If a given pathogen alone caused a disease, one would expect a 100% concurrence of the two factors. Absense of such concurrence obviously must be explained by the fact that there are other etiologically relevant factors in addition to the organism. Conversely, it is very rare that a clinical picture induced by a given organism (or other etiologic agent) is so typical that one can infer with certainty from the observed phenomena the nature of the pathogen involved. The defensive proccesses available to the host are sufficiently limited so that the same reaction may be called into operation in many situations.

Despite the obvious nature of these platitudes, we are all used to thinking in terms of etiology; i.e., that one factor may make the difference between the presence or absence of a given clinical syndrome. Not the least of the problems which plague us when we deal with schizophrenia has to do with these considerations.

In this paper three cases are presented. These patients were observed by the author and independently by at least one other psychiatrist. In each instance there was agreement that the patient was schizophrenic according to the criteria of the primary and secondary symptoms of Bleuler. The treatment in each case was distinct and in each instance apparently directed at etiologic factors. The results in all three, furthermore, were good.

Case Presentations

Case I. A.C. (Dr. C. Y. Bowers of the Ochsner Clinic and Dr. Kenneth Ritter have kindly allowed me to use their material concerning this patient.) This 17 year old girl was brought to my office by her mother. In manner she was vague and abstracted. Her speech was disconnected and confused. She felt people were watching and annoying her. She was much concerned with her parents' welfare. She confided that she spent a considerable amount of her time sitting by herself trying to figure things out. The onset of these complaints was abrupt. It occurred some three or four days before her visit. In the past, however, she was described as a relatively seclusive child, obedient and dutiful. She had few friends; she was a very conscientious student who hoped ultimately to study medicine. About a year earlier she had had a benign diffusely hyperplastic goiter removed by surgery. Aside from this the past medical history was negative. My impression was that the picture represented the onset of a schizophrenic psychosis and I advised that she be hospitalized. The family elected to consult Dr. Kemeth Ritter from whose notes and correspondence with Dr. Bowers, the remainder of this case report is abstracted. Four days after she came to my office, Dr. Ritter saw the patient in her home. She had been unable to sleep. Her speech was disconnected and dissociated. She was suspicious and apprehensive. Dr. Ritter's diagnosis was schizophrenic reaction, hebephrenic. At DePaul Hospital she was given electric shock and Serpasil. Her condition improved somewhat and she was discharged one month after admission with no change in diagnosis. For another month the patient seemed to do fairly well. Her presenting complaints then returned bit by bit. Two months after discharge she was noted to show much affective flattening. Her thinking was described as bizarre. About this time increasing weight gain and hirsuteness were noted. Six weeks later a total increase in weight of 20 pounds was recorded. The patient was referred to Dr. C. Y. Bowers at the Ochsner Clinic. He found her radioactive iodine uptake to be less than two per cent, and her protein bound iodine less than one gamma per 100 cc. Both of these values he considered compatible with myxedema. Treatment with thyroid extract has been accompanied by a steady improvement in this patient's mental condition. A note on May 23, 1956 (six months after start of thyroid treatment) states that she was attending secretarial school and enjoying it a great deal. She was dating regularly and in general was content. She remembered her psychosis vividly and was distressed by the recollection. One year later she was found to have maintained the remission.

This patient was seen by two psychiatrists each of whom found a typical hebephrenic schizophrenia. With the passing of time increasingly clear-cut evidence of an endocrinopathy evolved. When this was recognized and treated the psychotic syndrome went into remission.

Case II. W.H., a 39 year old man, was first seen in February 1950 as an in-patient at Charity Hospital, New Orleans. Admission was occasioned by

episodes in which he would "get tight all over and lose all sense of present and past. In about ten minutes he would come to himself at some place other than where the spell started. The seizures were preceded by the feeling that he was in the presence of ghosts. Although there were definite dscriptions of convulsive episodes, various observers had been of the opinion that these spells were functional. He was preoccupied with problems of religion and death. He described frequent vivid experiences—variable in content from time to time—but all involving his seeing and conversing with (among others) both God and the Devil. His fantasy life was filled with references to threatening and punishing figures. In manner he was vague and abstracted. Conversation was labored and communication difficult. How much of this was due to cultural factors and how much due to preoccupation was not clear. The present illness dated from his marriage ten years earlier. This had lasted about one month and was terminated by the wife because of his impotence. Since that time he had been content to live at home with his mother. He worked periodically as a laborer. An E.E.G. revealed "bitemporal spike foci." Neurological examination was within normal limits.

The patient was seen in a staff psychiatry conference where a primary diagnosis of schizophrenia was made. He was also considered to have true epilepsy and placed on regular doses of Dilantin. For approximately five years this man was followed at an epilepsy clinic. During this period he had few seizures and seemed to function at a level compatible with his origins and education. About one year ago he was placed on an experimental anticonvulsant drug we were then studying. Some two days after all of his previous medication (Dilantin and phenobarbital) was withdrawn, he was admitted to the locked ward at Charity Hospital. At this time he was in direct communication with God. He was in fact, serving as His messenger here on earth. He hallucinated continuously and was so insistent in his attempts to convert others that he had to be placed in seclusion. The experimental drug (since marketed under the trade name Peganone [Abbott]) was replaced by phenobarbital and Thorazine and these symptoms promptly cleared. The relation of his difficulties to the use of this new agent seemed so striking that the patient was again tried on the experimental drug and again with precisely the same results. The re-institution of phenobarbital alone again resulted in clearing up of his psychotic symptoms. He has been free of such episodes since.

In summary: This is a 39 year old man with E.E.G. evidence of brain damage, and a definite history of seizures. Inadequate anti-convulsant medication resulted in what was clinically a schizophrenic syndrome. Appropriate drug treatment was effective in relieving these symptoms.

Case III. M.A.W., a 30 year old lady was first seen by me in her home. A day or two prior to my visit her husband had terminated a three year long course of psychotherapy and a psychiatrist she had been seeing for a like period had become ill. Her reaction to these events had been to develop an intense degree of anxiety. This was manifested by gross body tremors as well as marked feelings of unreality. It was impossible for her to enter her bed-room. The walls seemed to close in on her. The drapes on her windows assumed weird and frightening shapes and colors. She hallucinated a powerful and lascivious colored man at her bedroom door. Objects about her as well as parts of her body seemed remote and different; she experienced micropsia. Windows in particular seemed threatening characteristics; in what appeared to have been a somnambulistic state she felt impelled to emulate Mary Martin in Peter Pan and fly. Her husband had to remove her from a second story window ledge on which she stood perched. When I saw her she was tense and anxious; there was visible tremor in her hands even at rest. She complained of air hunger. Her speech was disorganized and disconnected. The symptoms were so severe that she had to be hospitalized. Aside from sedation and Thorazine in the early weeks, treatment has been entirely by way of psychotherapy.

The patient is the only child of her mother and the second of her father. The half brother is some 16 years her senior. The parents are socially prominent and subscribe to all the usual prejudices associated with emphasis on social status. From her earliest days the patient was reared by a colored nurse, for whom she professed the most intense love. It was often necessary, however, to purchase this person's affection with what was called by the latter "love money." By definition this was any money the patient happened to possess. The mother was an alcoholic, a paregoric addict, and given to dramatic attempts at suicide. The father, an executive of a large corporation held his job because of his friendship with the president of the company and chairman of the board. This was known to the patient, but always regarded as a deep and most painful personal secret.

From the time (age 8) when she became aware of her mother's habits, the patient felt expected to care for her in her drunken episodes. Her father was wont to leave her at home with the mother because "he could not bear to deal with mother when she carried on like that." On this basis the patient accepted as not at all unreasonable the fact that at 11 she should manage the admission of mother into a mental hospital and that for some years following her discharge, she should have herself managed mother's nursing care—including the administration of hypodermics. Needless to say, in the mutual recriminating in which both parents indulged the patient was, alternatingly the confidante and ostensibly sympathetic listener for one or the other.

During her adolescent years there were only two people to whom she could turn for gratification of her own primitive anaclitic and more generally de-

pendent needs. They were the colored nurse and a paternal aunt. The former, a highly intelligent woman who resented bitterly her inferior status was the patient's nearly constant companion until she entered high school. Patient's feelings ran the gamut from violent, albeit unexpressed hatred, to abject devotion. A vignette from her 11th or 12th year epitomizes the relation. The nurse had brought the child to school and the latter insisted on kissing her as they parted. When the nurse objected that it was unseemly for a big white girl to be kissing a colored woman in public in this fashion, the patient replied, "I'll be black, too, if you will only love me." Even as she said this she was painfully aware of the falsehood.

The paternal aunt, a warm and loving woman, was a source of considerable embarrassment to the parents. Unlike her brother (patient's father) she had never risen above her relatively humble origin. She married a plumber and was content to lead a life appropriate to his status and income. Never, in this patient's memory was she or her husband invited to the parent's home. The patient, on the other hand, would frequently be sent to stay with the aunt when it suited the parents' convenience. Always extremely fond of her, the patient nonetheless experienced the same ambivalence in her feelings that plagued her relations with her nurse. Here was a person who was warm and protective, with whom she felt small and dependent. Yet, at the same time, in terms of her primary identifications with her parents, she (the aunt) was someone to be looked down upon with contempt and embarrassment.

The general principle was early established in this lady's life that her fruitful dependent relations had to be with people for whom she had contempt. To maintain such a relation; i.e., one in which she could be extremely dependent on someone all of whose weaknesses she detected and carefully catered to—was the principal adaptive problem of her life.

At eighteen she entered into a whirlwind courtship with a young naval flier. Fearful lest she be left an old maid she married him after less than six weeks acquaintance. Her husband proved to be subject to recurrent depressions. For ten years this lady had apparently maintained sanity by moulding herself to the neurotic needs of her husband. A few examples will suffice. For nine months during her 19th year she earned board and room for herself, her husband, and new-born baby by serving as cook and housemaid at a church rectory, the occupants of which were serving the war effort by making rooms available to another couple in addition to themselves and the patient and her family. Up to the time of her marriage a little over a year before, she had literally no experience with housework. During the post-war years she not only made equally as great sacrifices in living, but at the same time would step in for her husband and carry out his job as an insurance salesman at times when his depression became too deep. This kind of living, coupled with the bearing, nursing, and sole care, even including sewing the clothing, of three children made no noticeable dent in this lady's psychic equilibrium. To all intents and purposes she was a well adjusted and happy individual who took the difficulties of life as they came. She sought psychiatric help finally as much with the rationalization that she needed some guidance in dealing with her husband's depressions as with her own discomfort. Both husband and wife entered therapy. About a year after the former started treatment he showed considerable improvement in his functioning. As he improved, however, the wife became progressively more anxious. This culminated on the night of their wedding anniversary. In contrast to his usual feelings about this occasion, the husband proposed that they go out and celebrate the event. Two days before the date this ordinarily extremely graceful woman managed to jump very awkwardly, fall and break one of her tarsal bones. She was placed in a walking cast. On the night itself she was so frightened by her husband's gay expansive mood that she developed an acute anxiety reaction which not only necessitated cutting the evening short, but also required a visit from her therapist. As she later described the event, she was frightened not because her husband seemed well but because he seemed in his carefree "wiseguy" way to be saying that he had no need for her to take care of him; i.e., he therefore, had no need for her. During the following eight or nine months the husband experienced a recurrence of his depression. The patient during this period was able to get along quite well. She could express her feelings of anger towards the husband quite freely in therapeutic sessions and to some extent directly to her spouse. At no time, however, was there any change in the essentially "taking care of relation" she maintained with him. As he, however, again began to improve, the patient became again progressively more anxious. On the basis of discussions between patient's and husband's therapists, it was decided that the latter's improvement was sufficient to justify the patient's attempting a more dependent role with her spouse. This the patient undertook with much trepidation. On a vacation trip several hundred miles away from her doctor, the patient became acutely psychotic. When she returned to the city she had intense feelings of dread, horror, and unreality; she experienced micropsia. She hallucinated wild animals at her window, walls and objects in her room came and went. People changed size and form. All of this symptomatology was accompanied by the most intense degree of anxiety. Hospitalization was continued for nearly three months. Not the least of the factors contributing to the return of this lady's "sanity" was the husband's role in the simbiotic relation. As she became ill and he felt threatened by the possibility of her loss, his need for her became more explicit to himself and he began to display tender feelings and concern for her. Gradual improvement was brought to a halt by the sudden illness of her therapist which has been mentioned.

To summarize briefly the salient psychopathologic data, it has been this woman's conception that her most vital dependent needs have had to be gratified by people whom she held in some form of contempt; e.g., her weak alcoholic mother, her colored nurse, her very passive and at times inept husband and currently her psychiatrists, each of whose weaknesses she at once detected and catered to. Her procedure has been to ingratiate herself with each such person and to become indispensable to him as a price literally for being tolerated. She experienced any upsetting of this tenuous balance with extreme anxiety and the kind of disintegration already described. As in the course of therapy, this adaptive technique became more and more apparent to her and particularly in terms of ambivalent feelings for the therapist, she progressively improved. It has been possible both for her to discontinue therapy, and to maintain a much more satisfying relation with her husband and family than had ever been the case previously.

This lady on two occasions experienced acute schizophrenic episodes apparently as a reaction to circumstances which threatened the basis of her mode of adaptation to life. Treatment directed at an uncovering analysis of her adaptive techniques has resulted in considerable improvement in day to day functioning as well as relief from psychotic episodes.

Discussion

Even a cursory review of the literature indicates that these three patients are in no way exceptional. A case similar to case 1 has been reported by Wiltrakis and Portfilio.[1] Chambers[2] and Rodin et al.[3] are among those who most recently have cited instances analogous to case 2.

The etiologies which have been proposed for schizophrenia are many and varied. It is well known, for example, that Bleular's criteria for the diagnosis can be satisfied through the action of a large variety of drugs. Recently lysergic acid has received most attention in this regard, but it is not so long ago that bulbocapnine and mescaline were the rage in schizophrenia production. There is little doubt that the syndrome may be induced by pharmacologic means. That other etiologies are possible is the least one concludes from the welter of literature. To list the numerous suggestions which have been made hardly seems necessary. Bellak[4] tabulates no fewer than 39, and many of his categories are readily subdivisible. They include every possibility from purely genetic to purely environmental determinants. Every conceivable body system and nearly every kind of disease process (infectious, metabolic, degenerative) has been implicated. One is left with the feeling that either nearly everyone who has worked in this field has been all wrong, or else that there is some degree of validity in such radically different hypothetical formulations as the failure of the liver to obtain adequate blood supply as proposed by deJong[4] and a disturbance of the mother-child simbiotic relation as outlined by Sullivan[5] and Hill[6] among others. All these workers were, incidentally, primarily concerned with catatonia.

Of course, if one thinks of schizophrenia as a disease, this would seem on the face of it preposterous. On the other hand, it is, as is well known, not at all unusual for the same—or indistinguishably similar—symptom complexes to be secondary to radically different etiologic factors. What one deals with clinically is, after all, only the expression of a final common path, an end organ effect which could conceivably be put into action by a multitude of highly varying situations. Not all headaches are due to brain tumors, nor are they all secondary to inhibited rage. Epilepsy can result from, among other things, hypoglycemia, brain injury, tumors, and certain kinds of treatment of mental illness. The seizure does not represent a single disease, but rather an overcoming of the convulsive threshold of a given individual.

Again, by way of analogy, while it is certainly true that some people are more susceptible to seizures than others, it is equally true that no one is incapable of having convulsions and that for any given individual susceptibility varies enormously from time to time.

I raise the question, as Bellak[7] in effect already has, whether it might not be fruitful to consider what we call schizophrenia in a similar light. If the term is restricted so

that it refers to that which Bleuler[8] included in his primary and secondary symptoms, then the possibility of divergent etiologies is readily admissible. Many kinds of phenomena can impinge on the same final common path, and be experienced in precisely the same way.

It would not appear possible in any other way to reconcile the data presented in this report. Specific therapy directed at particular problems, one endocrine, one neurologic, and one purely psychologic, has resulted in the remission of a syndrome which, by clinical description was identical in all three cases.

One is tempted to go a step farther and suggest that the concept of schizophrenia may have outlived its clinical value. As it is used at this time it serves to confuse rather than to clarify. The implication of a discrete entity obscures the fact that all that has been demonstrated to be held in common by all people diagnosed as schizophrenic are certain manifestations, none of which has been proven to be primary phenomena. To the extent that they must be manifestations of some integrated nervous reactions of course no psychologic phenomena can be "primary." Would it not be of greater value simply to name these phenomena without the intervening assumption of the presence of a specific condition? To do so would tend to reduce the area of disagreement existing between the "dynamic" psychiatrist experienced with problems analogous to the present case 3, and the "biologic" psychiatrist for whom cases 1 and 2 may appear more convincing. It would underscore the fact that observations made on any particular group of psychotic individuals need not have relevance to others presenting the same type of symptoms but on other etiologic grounds. Brodie and Shore[9] seem to come to essentially the same conclusion. They state "The abundance of research with the tranquilizing and hallucinogenic drugs and with serotonin may not lead to a profound understanding of schizophrenia, but it may well result in a better comprehension of the integration of sub-cortical centers in the brain that regulate autonomic homeostatic mechanisms." Beres[10] in an exhaustive study of ego function in disturbed children seems to take the same position. He emphasizes repeatedly the importance of the phenomena observed and the fruitlessness of tying them to a particular nosologic entity with all that this implies concerning etiology and prognosis.

Summary

Three brief case reports are presented. These patients have in common only the fact that they had been diagnosed schizophrenia by at least two psychiatrists. In each case, therapy directed at a specific problem served to relieve the psychotic symptoms. It is proposed that schizophrenia is not a disease entity in the sense that it has a unique etiology, pathogenesis, etc., but that it represents the evocation of a final common path in the same sense as do headache, epilepsy, sore throat, or indeed any other symptom complex. It is further suggested that the term "schizophrenia" has outlived its usefulness and should be discarded.

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Experimental Studies of the Electroshock Process

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In the last seven years, increasing study by various authors[1-5] of the neurophysiologic alterations occurring in electroshock has resulted in a re-assessment of the mode of action of this form of therapy. The present neurophysiologic-adaptive hypothesis[1,2] states that an induced change in brain function provides the milieu in which behavioral changes can occur, depending upon the characterologic predisposition of the subject.

This report summarizes the data of three groups of studies which have been completed in the continuing evaluation of the electroshock process in this laboratory. These include:

1. The relation of changes in neurophysiologic indices to behavioral change;
2. Types of psychologic response expressed and factors in the evaluation of "improvement;" and
3. The role of personality in the behavioral response.

I. Subjects and Method:

The studies have been carried out in groups of consecutive, unselected electroshock referrals. The subjects are voluntary patients in an open ward psychiatric hospital. All patients are treated by resident psychiatrists, who make the referral to the electroshock therapy unit. The duration and type of therapy, however, are determined by the supervising psychiatrists in charge of the treatment unit. Patients varied in age from 20 to 66, and have been diagnosed as suffering from depressive and schizophrenic illnesses.

(a) *Tests of Brain Function:* Two indices of cerebral function have been stressed: Quantitative measures of the degree of induced delta activity in the electroencephalogram,[6] and changes in orientation and awareness of illness after amobarbital sodium.[7]

1) *EEG:* Electroencephalograms were done weekly prior to treatment, and on a day following a treatment. Bipolar recording was used, and selected leads were measured for the degree of delta activity. The average percent time delta for each of these selected leads, the highest delta index in any one lead, the highest amplitude and slowest frequency of delta, and the longest duration of bursts were the measures utilized in the classification of the records into "high degree," "moderate degree" and "low degree delta activity."[6]

2) *Amobarbital Test:* This is a structured interview, in which the patient is asked a standard set of questions pertaining to orientation and awareness of illness. Amobarbital is then administered intravenously, in a concentration based upon body weight, at a rate of 1 cc to every 40 seconds, until nystagmus and slurred speech are induced. In the initial series, a 5% solution of amobarbital was administered at the rate of 1 cc per minute. Recently, to permit simultaneous estimates of the sedation threshold,[8] the procedure was modified to allow for weight differences of subjects. The same questions are repeated, and persistent changes in orientation, denial of illness, confabulation, and reduplication are called "positive" and are indicative of states of altered cerebral function.[7] Tests were carried out before electroshock, and at weekly intervals during elestroshock on the day following treatment.

(b) *Evaluation of Behavior:* In addition to the notes of the patient's therapist and supervising psychiatrist, all patients were seen by the research psychiatrist at weekly intervals during treatment and 2-4 weeks after the last treatment. Evaluation of changes in behavior induced by electroshock were based on these descriptions. Ratings of improvement were based on the behavioral response two to three weeks after the last treatment, and reflect a short term clinical rating. The patients were divided into three groups: much improved, moderately improved and unimproved, based on criteria described.[2]

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(c) *Evaluation of Personality:* The initial method of personality assessment employed has been a structured family interview. In their original observations, Weinstein and Kahn described the characteristics of the "explicit verbal denial personality."[9] To determine the significance of this personality type for behavioral response, a structured questionnaire was developed. In interviews with two members of the family, the patient's usual attitudes and interests in 15 specific areas were explored. Each characteristic was rated as being absent, moderately present or markedly present. Scores of 0, 1 and 2, respectively, were assigned, and added—the resulting score being termed the "denial personality score."[10]

(d) *Treatment:* Electroshock was administered on a schedule of three treatments a week. A minimum of 12 treatments was given, except in a few cases where a severe confusional state appeared earlier. The course of treatment was determined by the supervising psychiatrist in charge of the electroshock unit, based upon clinical criteria. Treatments were grand mal, using either a Medcraft alternating current instrument or a Reiter C-47 electrostimulator. Patients were generally premedicated with intravenous Pentothal prior to the treatment.

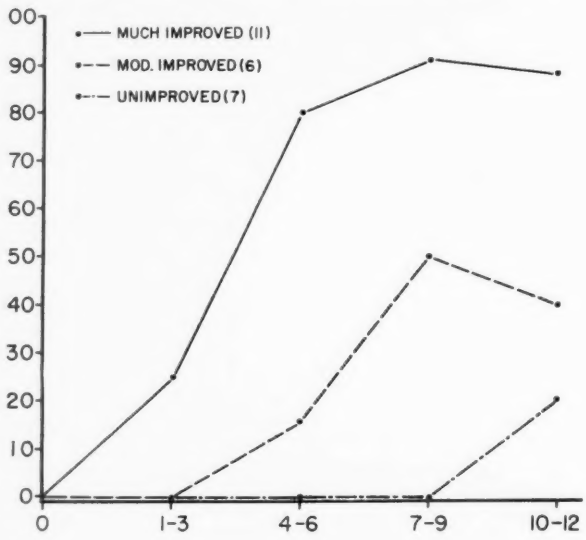
In the past year, a subconvulsive therapy group was instituted. Randomly selected electroshock referrals received 12-42 subconvulsive treatments, under Pentothal premedication. These patients were subjected to the same test procedures and the same behavioral evaluations as the grand mal therapy subjects. Neither the psychiatrist making the evaluation, the patient's therapist, nor the patient was cognizant of which patients received which form of therapy. The data for this series of patients is now being evaluated, and reference will be made only to the general observations.

II. Observations:

(a) *Role of Altered Cerebral Function in Behavior:*

1. Electroencephalogram:

In these studies, we have emphasized the degree of delta activity. In the initial series of patients a direct relationship was noted between the early development and maintenance of high degree delta activity and short term clinical ratings.[6] Of the patients who were rated much improved, 90% had high degree delta EEG records in the 3rd and 4th weeks of treatment, while of the unimproved patients, only 20% had such records. The relationship between delta activity and clinical ratings is seen in Figure 1.



In subsequent series, these observations were extended in a predictive study. Based on the earlier observations, it was suggested that the much improved patients were those in whom high degree delta activity had been induced early in the course of treatment and sustained. Records during the second and third weeks of treatment, therefore, were assessed. The results in 54 consecutive patients are noted in Table I. Of the patients who developed high degree delta activity during the second and third weeks of treatment, 67% were rated much improved, while only 30% of the patients without such activity were so rated.

TABLE I

Patients With High Delta Activity During Second, Third Weeks of Treatment

	CLINICAL RATING		
EEG Delta	Much Improved	Moderately Improved	Unimproved
Both High (18)	12 (67%)	4 (22%)	2 (11%)
One High (16)	4 (25%)	8 (50%)	4 (25%)
None High (20)	6 (30%)	7 (35%)	7 (35%)

2. Amobarbital Test:

In the initial series of 24 patients, previously reported,[2] eleven patients were rated as much improved, and all had positive amobarbital test reactions after 7 to 9 treatments and sustained this response. Of the unimproved patients, 15% had positive amobarbital responses in the third week and 28% in the fourth week, but these were not sustained.

A comparison of both the EEG observations and the amobarbital test data, as related to the eventual clinical rating is seen in Table II. In 77 patients tested to date, observations during the second and third weeks of treatment were examined for the presence of high degree delta activity and positive amobarbital test results. Of the much improved patients, 75% had both positive amobarbital tests and high EEG delta activity during this period. Of the unimproved patients, however, 57% had neither positive amobarbital tests nor high EEG delta activity. It is apparent that the cluster of positive amobarbital tests, high EEG delta activity and much improved clinical ratings is a significant one; and equally significant is the cluster of negative amobarbital tests, low and moderate EEG delta activity and clinical rating of unimproved.

TABLE II

*EEG and Amobarbital Test Results During Second, Third Weeks of Treatment**

	Much Improved	Moderately Improved	Unimproved
Both Positive Amobarbital and High EEG Delta Activity	25	10	3
Either Positive Amobarbital or High EEG Delta Activity	8	12	5
Neither Positive Amobarbital nor High EEG Delta Activity	0	3	11
Total	33	25	19

*Significant at better than .01 level of confidence.

(b) *Clinical Patterns of Behavior:*

In these patients, we have observed varied responses to electroshock including the absence of noticeable symptoms with a return of pre-morbid behavior; hypomania, euphoria, and denial; paranoid states with ideas of reference and delusional formation; confusional states with varying degrees of memory disturbance; increased somatic complaints and preoccupations, states of increased panic, excitement and agitation and varying degrees of withdrawal, and seclusiveness. The degree of behavioral change is seen to be related to the degree of alteration in the neurophysiologic indices. During electroshock, with the gradual induction of states of altered brain function, and their restitution in the weeks following cessation of therapy, behavior shows characteristic patterns. The following are but a few of the gross patterns that are observed during the period of increasing and waning states of altered brain function.

An early change in behavior in retarded subjects, for example, may be a change in the degree of participation in ward activities and increased neatness and interest in personal care. This is succeeded by a phase of minimizing symptoms and displacement of complaints, mild euphoria, denial of illness, and insistence upon going home. At this time, the EEG shows the greatest degree of delta activity and amobarbital tests are positive. With the cessation of treatment, the overactivity diminishes, and interest in the future becomes prominent. Premorbid patterns of behavior are in evidence, and the EEG returns to normal and the amobarbital test becomes negative.

Other depressed subjects, however, become increasingly disturbed during treatment, withdraw from participation in hospital activities, and complain increasingly of memory loss, physical distress and insomnia. Amobarbital tests and electroencephalograms may show the same degree of change as in the first group. With cessation of treatment, there is either a return to the depressed state, or a persistent emphasis on the memory loss and physical complaints of the treatment.

Another pattern, seen in hostile, negativistic and withdrawn patients, is the development of hyperactive, hypomanic, and impulsive behavior. Memory loss is marked, and clinical disorientation and confusion may be noted at the height of neurophysiologic change. After treatment is ended, ideas of reference, negativism and delusional for-

mation become prominent, to be followed by withdrawal and mutism.

(c) *Effect of Subconvulsive Therapy:*

The interdependence of these adaptive patterns with the state of altered brain function is more clearly demonstrated by observations in the subconvulsive group. Twenty-seven subjects received subconvulsive therapy instead of grand mal. Minimal changes in the electroencephalogram and in amobarbital tests were induced, and the changes in clinical behavior were limited. The electroencephalograms demonstrated either no delta or a minimal amount of such activity. In no patient were moderate or high degree delta activity records observed. In the amobarbital tests, only three patients had positive tests during treatment, and in each instance it occurred only once. No change in symptoms or behavior was noted in twenty-three. Nineteen were referred for a second course of treatment. Grand mal electroshock induced changes in brain function of high degree delta activity and/or repeated positive amobarbital tests in fourteen of these. All fourteen showed significant changes in behavior; while of the five patients in whom the physiologic indices showed only minor changes, only two patients showed a definite behavioral change.

(d) *Role of Personality in the Adaptive Response:*

Another variable in the adaptive response of the patients is the personality—the habitual attitudes, patterns of perception and behavior and defenses of the patient. The initial study of the role of personality related the characterological disposition of patients showing denial mechanisms to the clinical result. The relatives of 47 patients were interviewed, and denial personality scores assessed. Scores ranged from 0 to 25, with a median of 11. The scores were divided into two groups: scores from 11 to 25 were classed as the "high denial group" and those from 0-10 as the "low denial group."

Of the patients with high denial personality scores (Table III), 58% were in the much improved group, and only one patient (4%) was in the unimproved group. The ratings of improvement for the patients with low denial personality scores were random—about one third appearing in each rating category.

TABLE III

Relation of Denial Personality Scores to Clinical Response to Electroshock

Personality Score	Much Improved	Moderately Improved	Unimproved	Total
11-25	14	9	1	24
0-10	7	9	7	23
Total	21	18	8	47

The difference in the denial scores between the much or the moderately improved patients, when compared to the unimproved patients, is statistically significant.

That the personality ratings were indeed reflective of the patients' adaptive response under the conditions of altered brain function is noted in the correlation of these scores with actual changes in language patterns which had been described[11] as indicative of denial responses. As in that study, changes in language in structured interviews with the patient were studied. Each patient was classified according to whether he showed three or more explicit language changes. The group of patients with high denial personality scores showed a significantly greater number of language changes than patients with low personality scores. The coefficient of correlation is +.71, which is significant at better than the 1% level of confidence.

III. Discussion:

These studies of the neurophysiologic and psychologic aspects of electroshock support and amplify the hypothesis of electroshock action initially expressed by Weinstein, Linn and Kahn,[1] and again by Kahn, Fink and Weinstein,[2] and the observations of Roth,[3] Aird,[4] and Ulett.[5a, b] Alteration in brain function is the central effect of electroshock therapy, and is a pre-requisite to behavioral change. We have emphasized delta activity in the electroencephalogram and the patterns of disorientation, confabulation, and denial of illness after amobarbital as indices of altered brain function. Other measures, applied in the same serial fashion, will, we believe, demonstrate the same relation to changes in behavior or alteration in brain function.

Under the conditions of the induced

change in brain function, altered patterns of adaptation are expressed. The type of adaptation varies, apparently dependent upon the personality organization. In these studies we have noted the relationship of an "explicit verbal denial" personality type with the development and maintenance of clinical language patterns of denial, displacement, and minimization in structured interviews.[11] We have observed that patients with high denial scores are those who are more likely to be evaluated as "much improved" (Table III). The type of adaptation is varied, however, as we have described here. In this context, therefore, the conclusion is affirmed that electroshock is a means of inducing change in cerebral function in which altered patterns of adaptive-interpersonal behavior can be sustained.

We have emphasized "change in behavior" in this report. In previous studies, we related our observation to "improvement." "Improvement" is a derivative evaluation of the induced behavioral change, which is dependent upon the expectations of the therapist, the family, or the administrator, in the milieu in which the behavior is observed. When a depressed patient, who had been withdrawn, crying, and had expressed suicidal thoughts, no longer is seclusive, and is jovial, friendly and euphoric, denies his problems and sees his previous thoughts of suicide as "silly," a rating of "much improved" is made. To the extent that a schizophrenic patient is perceived as less delusional, less excited, and less withdrawn, he is rated as "improved." When, however, the induced behavior is one of increased anxiety and fearfulness, or persistent complaints about memory loss, pain or other physical symptoms, or excitement and delusional thoughts, a rating of "unimproved" will be made.

These studies amplify the present neurophysiologic-adaptive hypothesis of electroshock action. Further studies, defining the significant aspects of personality and of the expectations of the environment on the patterns of behavior which are observed under the condition of altered brain function are suggested. Application of this hypothesis to the effect of newer tranquilizing agents is in progress. Finally, studies of individual differences in the neurophysiologic response to equivalent amounts of cerebral trauma warrants exploration.

IV. Summary and Conclusions:

1. This report summarizes continuing experimental studies of the mode of action of electroshock therapy.

2. Behavioral change in electroshock is dependent upon an alteration in brain function as evidenced by serial changes in delta activity in the electroencephalogram and disorientation and confabulation with intravenous amobarbital.

3. The pattern of behavioral alteration is shown to vary markedly, depending upon the degree of induced cerebral dysfunction, the personality of the subject and the environmental situation.

4. "Improvement" ratings are seen as a special case of behavioral change dependent upon the type of adaptation elicited, the expectation of the therapist, administrator and family, and the tolerance of the milieu.

5. The extension of this neurophysiologic-adaptive hypothesis of electroshock action to other forms of somatic therapies is suggested.

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Prochlorperazine in Hospitalized and Private Psychiatric Patients

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Studies in animals showed that prochlorperazine, a new phenothiazine compound, blocks conditioned reflex response as effectively as chlorpromazine, can be given in lower doses, and has less effect on spontaneous motor activity.[1] Clinical trials established the usefulness of the compound in relieving mild anxiety and tension states, and uncovered no evidence of jaundice, blood dyscrasias, or hypotension.[2,3] Preliminary studies of the drug in hospitalized patients indicated its usefulness in controlling marked psychomotor excitement and provided further evidence of its relative safety.[4,5] These findings prompted me, in April 1957, to start a pilot series with prochlorperazine and later, on finding the drug effective, to extend its use at the hospital and in private practice. While approximately 700 patients received prochlorperazine on our services, this report concerns itself with a cross-section of the types of patients commonly seen in hospital and office work.

Material

Our series of 109 patients, summarized in the table, included acute and chronic psychotics, psychoneurotics, patients with tension states, and children with behavior problems. The psychotics were assaultive, denudative, overactive, deluded, confused, and generally speaking, difficult management problems. The psychoneurotics manifested a mounting uneasiness of mind, heightened tension, and a host of somatic complaints, including headache, insomnia, vertigo, gastrointestinal disorders, eczema, asthma, and various allergies. The group was just about evenly divided between men and women, and ranged in age from 12 to 100 years. Most, however, were between 30 and 50 years. Duration of illness ranged from several months to 15 years or more in the psychotics, and from one month to five years in the psychoneurotics and children. About half of the group, chiefly the chronic psychotics, had been treated previously with sedatives, other neuroleptic agents, and ECT, but failed to show or maintain any appreciable improvement. The untreated patients included the disturbed children and those with tension, psychoneurosis, and acute schizophrenia. Except for manic depressives and acute schizophrenics, the patients received prochlorperazine in conjunction with supportive psychotherapeutic measures; the exceptions were given ECT too.

Method

Patients, before being placed on prochlorperazine, were given a complete physical examination and followed, periodically, with blood and urine studies. Most were started on oral medication, 10 mg., to be taken at meals and at bedtime. Dosage was increased gradually in increments of 10-20 mg. every other day until clinical improvement resulted or bothersome side effects supervened. When rapid control of agitation and excitement was necessary, prochlorperazine was given

From the Oregon State Hospital, Salem, Oregon.

intramuscularly, 10-20 mg., repeated every three to four hours, as necessary. Although dosages as high as 300 mg. were given, the usual oral maintenance dosage was 75-150 mg. for psychotics and 30-75 mg. for psychoneurotics. As a matter of convenience, patients, once stabilized on prochlorperazine, were given the drug in sustained release capsule form. These capsules contain the drug prepared as hundreds of tiny pellets, some of which were uncoated and some coated with varying thicknesses of a digestible film. The uncoated pellets disintegrate promptly to provide a therapeutic effect shortly after ingestion while the coated pellets disintegrate at a slowed but gradual rate to sustain the initial therapeutic effect approximately twelve hours. This form spared the nursing staff the inconvenience of administering the drug and the private patients of having to remember to take their medicine at more frequent intervals.

Hospitalized patients, aside from being seen daily by nursing personnel, were interviewed weekly by staff physicians to determine behavior changes and to adjust dosage, as necessary. Private patients returned after a week's trial on prochlorperazine. Those who tolerated the drug or who benefited from taking it were continued on it and, thereafter, seen every two or three weeks, depending on their need for counselling. Some patients showing a good progress simply phoned periodically and, with reassurance and encouragement, were able to extend their time between visits to 4 and occasionally 6 weeks. No special laboratory studies to detect jaundice or agranulocytosis were run since we share the belief of Goldman[5] that these untoward reactions can be uncovered readily from clinical signs and symptoms.

Results

Patient response was graded *A, B, C,* or *D.* In hospitalized patients, *A* meant the subsidence of all active psychotic manifestations, loss of overt hostility, attainment of socially acceptable affect, and capacity for full-time employment; *B* meant a good social recovery, that is, patients, although harboring some delusions, could be returned to society, earn a living, and stand up to the ordinary stresses of everyday life; *C* meant complete or appreciable reduction of assaultiveness, denudativeness, hyperactivity without substantial decrease in delusions or hallucinations; *D* meant little or no improvement. In patients from private practice, *A* meant they recovered from overt symptoms, were functioning well socially, and appeared capable of withstanding situational problems; *B* meant they were essentially symptom-free, were gaining insight, and could be expected to face environmental stress without folding; *C* meant their anxiety lessened, initial symptoms decreased in intensity, and prognosis seemed good even though social skills remained statically low; *D* meant little or no improvement.

The table summarizes our results and shows that prochlorperazine proved effec-

TABLE I

Classification and Results of Treatment in Patients Given Prochlorperazine

Diagnosis	No. of Pts.	Aver. Dosage	Efficacy A	B	C	D	Remarks
PSYCHOSES							
Acute Schizophrenia	28	25 mg., t.i.d.	26	–	–	2	Given ECT and prochlorperazine.
Manic Depressive	6	25 mg., t i d.	6	–	–	–	"A" patients discharged within 8 weeks.
Chronic Schizophrenia (15 years' duration)	27	75 mg., b.i.d.	14	2	8	3	Improving slowly; quieter, easier to manage.
CBS with Psychosis	27	10-25 mg., 2 or 3x	22	–	5	–	Less agitated, restless.
PSYCHONEUROTICS							
Mild Tension	10	10 mg., t.i.d.	7	–	–	3	All patients receiving supportive psychotherapy in conjunction with prochlorperazine.
Conversion States	4	25 mg., t.i.d.	–	4	–	–	
Compulsive Neurosis	1	25 mg., t.i.d.	–	1	–	–	
Anxiety States	2	25 mg., t.i.d.	–	2	–	–	
Behavior Disorders (Children)	4	10 mg., t.i.d.	2	2	–	–	

tive in severe as well as mild mental and emotional disorders. As might be expected, best results in hospitalized psychotics occurred in acute schizophrenics who received prochlorperazine in conjunction with ECT. Many, perhaps all, would have responded to ECT alone, but on combined prochlorperazine-ECT, they were more comfortable, less apprehensive and tense, and more accessible to counselling than those given ECT alone. No episodes of vasomotor collapse or other untoward reactions occurred with combined prochlorperazine-ECT therapy. Using prochlorperazine to keep the patient calm between shock treatments appeared to hasten recovery without running additional risks. Moreover, patients continued on prochlorperazine after their discharge were, when interviewed eight months later, adjusting to conflicts in environment and personal relationships that had previously been too much for them to cope with. While it is still too early to reach any conclusions, our experience to date indicates that giving prochlorperazine to discharged patients reinforces the gains made during their hospitalization. Up to the present writing none of the acute patients discharged on prochlorperazine have relapsed. This preliminary observation parallels those of Kris[6] and Pollack[7] who have successfully used chlorpromazine to reduce substantially the rate of relapse in discharged mental patients.

Less dramatic but more rewarding were the responses in chronic schizophrenics, that is, in those who had been hospitalized for 15 years and more. Their improvements in neatness, eating habits, and general behavior leave much room for further improvement before these patients can go home; however, their chances of getting to go home are very much greater. Just how many of these patients can be returned to society will depend, in large measure, on the effectiveness of our psychotherapeutic program, our enlisting family support, and eventually providing counselling in aftercare clinics. (It is well worth noting that even nominal gains in a few chronic patients often do much to boost the morale of psychiatric nursing personnel. Undoubtedly, such gains have helped reduce the turn-over in these dedicated people.)

In the high dosage needed to control excited psychotics, extrapyramidal symptoms were encountered in about 20 per cent of the group. Gaining experience with the drug revealed that the appearance of such symptoms usually heralded a favorable response. When symptoms became bothersome to the patient, they could be controlled by giving anti-Parkinsonian agents concomitantly (Kemadrin 5 mg., t.i.d.) or by reducing the dosage of prochlorperazine. Oddly enough, some patients who from signs of tremulousness, drooling, and masked facies appeared distressed, told of being calmer and more relaxed than they had been before prochlorperazine therapy was started. No evidence of liver dysfunction, blood dyscrasias, hypotensive episodes, skin disorders, or untoward reactions was observed.

Prochlorperazine quickly brought under control agitated patients with CBS associated with senility and arteriosclerosis. Twenty-two of the 27 aged patients in this series became models of good deportment, in marked contrast to their pretreatment restiveness, confusion, and destructiveness. In the others, improvement was somewhat offset by what seemed to be a stimulant effect of the drug, which caused existing sleep problems to be aggravated and required giving a mild sedative at bedtime. During the daytime, the stimulant effect was evident in some patients as brightened spirits and mental alertness. Thus, use of the drug in aged ambulatory patients, in moderate dosage, appears free of drawbacks ordinarily associated with tranquilizing therapy—undue drowsiness and vasomotor disturbances—and should reduce the rising number of such patients admitted to state hospitals each year.

Fourteen of the 17 private psychiatric patients benefited from prochlorperazine given in conjunction with supportive measures such as persuasion, encouragement, sympathy, and reassurance. To be sure, the drug did not resolve emotional conflicts, but by reducing anxiety and tension, it paved the way for the therapist to keep control of the patient while helping him to cope with situational problems and to compensate for handicaps. Symptomatic relief from chronic stress and strain imposed by the fast tempo

of modern living enabled tired business men, bored housewives, frustrated career girls, and others to enter quickly into, and profit from, counselling that otherwise might have been prolonged and possibly unproductive.

Prochlorperazine's onset of action proved rapid, even with oral medication: patients reported some symptomatic relief usually within two or three days after starting the drug. Continuing the drug generally produced further gains. No drowsy side effects were noted. In fact, Lehman and Csank[8] found that prochlorperazine behaved like a stimulant in psychomotor performance studies, improving reaction time and increasing hand steadiness. This property, which is uncommon in neuroleptic agents, is a definite asset in treating ambulatory patients.

While only four children with behavior disorders were given prochlorperazine their favorable responses indicate further trial of the drug in such cases is warranted. In general, the children became quiet and less active, took interest in their schoolwork, and were reasonably well behaved at home and in school. No side effects were observed.

Generally speaking, patients with hypernormal drive, uncontrolled impulsivity, and emotional excitement derived the most symptomatic relief. And, again generalizing, degree of response depended in large measure on the flexibility of the patient and his environment. Use of prochlorperazine effectively reduced the level of anxiety, making the patient more quickly available for psychotherapy. Once in therapy, patients continuing the drug were better able to weather the anxiety and tension that frequently mounted when they began to gain insight into their illnesses.

Summary

Prochlorperazine, studied in 109 psychiatric patients for eight months, proved effective in controlling psychotic manifestations of severely disturbed patients and in reducing mounting tension and anxiety of psychoneurotic patients. No untoward reactions of jaundice, agranulocytosis, and hypotension attributable to the drug were observed. Combined use with ECT appeared safe as well as beneficial to relieve agitation and excitement. Extrapyramidal symptoms such as tremulousness, drooling, and masked facies occurred in excited psychotics on high dosages (100-300 mg.); giving anti-Parkinsonian agents concomitantly or reducing dosage usually provided relief. In lower dosages, given ambulatory patients, drowsy side effects were absent; in fact, a few patients appeared stimulated on taking prochlorperazine. Use of the drug in sustained release Spansule form provided, with one capsule, a therapeutic effect that lasted approximately twelve hours.

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Author's Note: Prochlorperazine (Compazine) tablets and 30 and 75 mg sustained release capsules were supplied for investigational use by Smith, Kline & French Labs., Phila., Pa. The 75 mg sustained release capsules are not yet commercially available.

Combined Ritalin and Serpasil Therapy in Chronic Psychoses

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It is estimated that approximately 60% of the population in state hospitals consists of chronic cases, predominantly regressed schizophrenics, hospitalized for many years. In the majority of these cases, electro-convulsive therapy, insulin coma and subcoma therapy have failed. Without dramatizing the therapeutic results of various chemical substances in the treatment of chronic psychiatric disorders, they have replaced more drastic forms of therapy with less risk to the patient and doubtless, with better results.

Selection of Cases

All the cases included in this study consisted of chronic, regressed and deteriorated patients, with a minimal hospitalization of 3 to a 15 year maximal. More than 70% had received electro-convulsive therapy and/or insulin coma therapy without permanent improvement; 40% were on a maintenance dose of electro-convulsive therapy and 30% on insulin subcoma therapy, only to control their aggressive and destructive behavior. The majority of patients were in the age group of 30 to 50; the youngest patient 14 and the oldest 75 years of age.

The patients selected for this comparative study were divided into three groups:

GROUP A. Consisted of 40 patients, all but one were chronic and regressed schizophrenics with a history of hospitalization of 3 to 15 years—these patients received methylphenidate (Ritalin) only.

GROUP B. Consisted of 80 chronic schizophrenic patients, used for comparative observation and evaluation. The clinical evaluation of this group was reported previously.[28,29] These patients received reserpine only.

GROUP C. The largest group consisted of 100 chronic psychotic patients, and were selected for combined treatment with reserpine and methylphenidate (Ritalin). Among these patients over 50% failed to respond to other forms of chemotherapies, including methylphenidate, or relapsed after being discontinued from chemotherapy.

As shown below, 84% of the patients in this group were chronic, deteriorated and regressed schizophrenics.

From Rockland State Hospital, Orangeburg, N. Y.

TABLE 1—*Diagnostic Classification on Group A*

Dementia Praecox, Catatonic	12
Dementia Praecox, Hebephrenic	8
Dementia Praecox, Paranoid	10
Dementia Praecox, Mixed	9
Involutional Psychosis, Melancholia	1
Total	40

TABLE 2—*Diagnostic Classification of Group B*

Dementia Praecox, Catatonic	30
Dementia Praecox, Hebephrenic	12
Dementia Praecox, Paranoid	20
Dementia Praecox, Mixed	10
Other Types (Childhood Schizophrenia)	4
Psychosis with Cerebral Arteriosclerosis	4
Total	80

TABLE 3—*Diagnostic Classification of Group C*

Dementia Praecox, Catatonic	22
Dementia Praecox, Hebephrenic	30
Dementia Praecox, Paranoid	10
Dementia Praecox, Mixed	20
Childhood Schizophrenia	2
Psychosis with Mental Deficiency	6
Organic Psychosis	4
Psychosis with Epilepsy	3
Involutional Psychosis	2
Manic Depressive, Depressive	1
Total	100

In Group C, among the patients diagnosed as organic psychosis, two patients were chronic general paretics with paranoid delusions, episodes of assaultive behavior and had moderate hypertension; the other two were diagnosed as psychoses with cerebral arteriosclerosis and had marked hypertension. In view of Carter's report[3] of favorable results in the treatment of certain mentally defectives and epileptics, we selected for combined treatment with reserpine and methylphenidate, six patients with mental deficiency, ranging from low grade imbeciles to morons, with superimposed psychoses, and three patients diagnosed as psychoses

with epilepsy who, in addition to psychotic manifestations such as hallucinations and delusions, have undergone very definite deterioration and some had frequent episodes of impulsive, assaultive behavior. The seizures were kept under control by proper anticonvulsive medication in all but one patient.

TABLE 4—*Distribution of Cases in Groups A, B, and C as to Duration of Hospitalization*

	3-5 yrs.	5-10 yrs.	10-15 yrs.	Total
Group A	12	18	10	40
Group B	25	39	16	80
Group C	36	40	24	100
Total	73	97	50	220

Methods of Study

It is well recognized that an intensified therapy program in large mental institutions depends upon team work and close cooperation between the physician, the ward personnel, the occupational therapist, etc.; that everyone contributes to the ultimate benefit of the patient. Recognizing the importance of this factor in a large scale, long term drug evaluation, the senior author, over the period of the past three years, had regular monthly round table conferences with the ward personnel. In these meetings they were oriented with all aspects of the project. We observed that such round table discussions, not only aroused the individual interest of the personnel, but moreover, resulted in team work. In addition, such meetings contribute to the training of the psychiatric nursing personnel, keeping up with progress and advancement in the psychiatric treatment.

This brings up the question of the true double blind experiment in this type of investigation. While it is indisputable that the double blind experimental method has its scientific justification, yet in our observation and in that of others, Gruber, et al.,[9] it has its limitations, mainly on large scale studies with new chemotherapeutic compounds. It is likely to create confusion and in timely protracted studies, the observers have a fairly good idea at what time which substance is being used. Thus, the basic idea of the double blind experiment is eliminated per se. We observed that when the ward personnel is properly indoctrinated in respect to all phases of a project, their reports are just as objective, if not more so, than if they merely were carrying out orders without knowing anything about the drug being used.

Another factor which is rarely thought of in testing the therapeutic effectiveness of a new compound by the crossover-double blind method, mainly in chronic cases, is the question of whether or not the interruption of the medication for a period of several weeks and then restarting it, may possibly influence the final effectiveness of the drug in a negative sense.

Prior to starting the treatment, every patient had a complete physical examination and clinical laboratory studies such as CBC, urine analysis, liver function and blood sugar were checked at weekly intervals. In a few patients in Group B, the acidity of the stomach content was followed.

The patient's mental condition is evaluated regularly by the physician, as well as from regular reports of the ward personnel and occupational therapist. Those patients whose condition improved sufficiently to be considered for release from the hospital are also screened by a separate medical staff.

Dosage and Mode of Administration

Patients in Group A, on methylphenidate only, were divided into two equal sub-groups, each of 20 patients. One group was on oral medication only, while the other was on injectable and oral. In order to observe and compare the pharmacodynamic effects of the substance we started out with relatively high dosages. The group selected for oral medication was administered 40 mg. t.i.d. for the first 3 to 4 days and the group on parenteral administration, 30 mg. i.m. t.i.d. The dosage was then gradually decreased so that at the end of the second week both groups were adjusted on 20 mg. t.i.d. We soon observed that individualization and frequent changes of dosage were necessary. If no untoward side effects occurred, necessitating change of dosage or discontinuation of therapy by the end of the fourth week, the dosage was decreased to 20 mg. b.i.d. and, at the end of the sixth week to 10 mg. t.i.d. After the eighth week the patients were kept, unless change in their condition required an ad-

justment, on 10 mg. b.i.d. for a period of one to two months.

The patients in Group B were started on 5 mg. of reserpine parenterally and 3 mg. orally o.d. The dosage was gradually decreased so that by the end of the 5th week the patient received 3 mg. o.d. orally. The oral dosage was decreased slowly, so that by the end of the 10th to 12th week, the patients received only 1 to 2 mg. o.d. Occasional adjustments of the dosage were required according to the degree of side effects and the patient's therapeutic response. In the treatment of chronic schizophrenics, it is preferable to start with a high dose, then attempt to decrease the dosage gradually, and from practical experience, we learned that the treatment should be carried on at least for 6 months.

The patients in Group C, on combined therapy with reserpine and methylphenidate, were started on 3 mg. of reserpine o.d. orally and 20 mg. of methylphenidate t.i.d. orally. If a patient showed increased restlessness or marked anorexia, he was given 5 mg. of reserpine intramuscularly, two or three times a week. This was necessary in about half of the patients during the first two weeks. We set the initial maximal dosage of methylphenidate at 20 mg. t.i.d. orally, due to the fact that experience showed that dosages higher than 60 mg. daily were not desirable, in view of the fact that the stimulating effect of the substance as compared with the dosage, follows an exponential curve.

If the patient's physical and mental condition did not indicate individual adjustment, the total dosage of both drugs was gradually decreased so that at the end of the eighth week he was given 2 mg. of reserpine, orally o.d., and 10 mg. of methylphenidate, orally t.i.d. The predominant reserpine effect can be easily checked by an appropriate increase of the daily dosage of methylphenidate and on the other hand, predominant methylphenidate effect can be checked by increased reserpine dosage.

In the majority of cases on combined therapy, we observed that individual changes of dosage were much less frequently needed than in patients on either of the drugs alone. In several cases the patients were able to maintain a certain level of improvement only if kept on a maintenance dose for a prolonged period of time. We learned that the lowest maintenance dose was from 10 to 20 mg. methylphenidate o.d. and 1 to 2 mg. reserpine o.d. We had a few patients who were kept on a maintenance dose for about a year without showing any serious complications.

With methylphenidate, similar to other observers,[3,5,6,17] we noticed that the optimal dosage ranges from 10 to 20 mg. t.i.d.

It is important in the chemotherapy of chronic patients that they should be kept on medication for at least six months. An early interruption of treatment in these chronic cases, although the patient shows improvement, frequently results in a relapse of their condition. Similarly, a rapid decrease of the dosage over a relatively short period of time, may result in failure. Repeated courses of therapy will bring about improvement in some of the failures.

Pharmacodynamic Evaluation

In order to evaluate a compound or combination of compounds one has to become familiar with its pharmacodynamic effects and chemical properties. From our observations on several hundred chronic schizophrenic patients treated with various chemotherapeutic agents, we came to the conclusion that certain basic schizophrenic features are seldom, if at all, altered by chemotherapy. Those features which seem to be anchored in the patient's premorbid personality, obviously become accentuated and manifest to a pathological degree, so that they are clinically an integral part of the schizophrenic process. A schizophrenic patient, even showing marked improvement in response to chemotherapy, will retain shallowness or flattening, or, some inappropriateness of his affect. He will remain basically seclusive and continue to have difficulties in forming proper interpersonal relationship; and will retain an exaggerated suspicion in contact with his environment.

This is not surprising if we consider the psychosis as emerging out of a schizoid premorbid personality. It would be utopistic to expect to alter the basic personality structure by some chemical means. On the other

hand there is sufficient evidence that various chemotherapeutic agents used in the treatment of psychiatric disorders greatly influence, beneficially, the overt psychotic symptomatology. It is also true that the beneficial therapeutic results with these chemical compounds are due to the effect on the biochemical processes of the central nervous system either directly or via some secondary metabolic changes. There can be little doubt that the beneficial therapeutic results on the outward manifested psychotic symptoms have to be logically due to some reparative changes in the central nervous system, induced or caused by the pharmacodynamic properties of the drugs.

In combined therapy the pharmacodynamic synergism or antagonism is of prime importance in adjusting the proper dosage and in the evaluation of side effects, as well as probability of the therapeutic results.

In animal experiments with reserpine, the most marked effect is a state of relaxation and sedation. There is a wide range of responsiveness in animals. Cats, rats and dogs require a much smaller dosage of reserpine than do monkeys and humans, to achieve the same pharmacodynamic effect. Evidently the higher the degree of differentiation of the central nervous system, the higher is the effective dosage of reserpine required.[22] This fact may explain why it is necessary to use a relatively high dosage of reserpine to achieve the proper therapeutic response, and also, some of the somatic as well as psychic side effects are more prominent in man than in experimental animals. Actually, some of the side effects were first observed and described in man and not in experimental animals. From a clinical point of view the most important side effects are the depressive states, the Parkinson-like symptoms and the typical "turbulent phase," as first described by Barsa,[2] in a report of psychotic patients and since observed and evaluated by others.[12,13,28,29]

During the early days of reserpine therapy in the treatment of psychoses, the onset of the "turbulent phase" with its activation of the psychotic symptoms, some restlessness as well as occasionally observed aggressive behavior, was considered to be an unfavorable sign and the treatment was frequently discontinued. Contrary to this, it appears that the "turbulent phase" during reserpine therapy, as observed on a large number of acute and chronic schizophrenics, should be considered prognostically a favorable sign and the therapy should not be discontinued, but if necessary, the dosage temporarily increased.

In Group B patients, where 95% were chronic, regressed and deteriorated schizophrenics—with respect to the "turbulent phase" as a release phenomenon, we made the following interesting observation. First, comparing with acute cases, the onset of the "turbulent phase" in chronic cases is chronologically definitely delayed. Second, there seems to be a relationship between the intensity of the "turbulent phase" and the ultimate therapeutic results. Those patients with a marked "turbulent phase" ultimately showed a higher level of improvement.

TABLE 5—*Onset of the "Turbulent Phase" in Relation to Weeks of Reserpine Therapy*

Total No. Pts.	1st week	2nd week	3rd week	4th week	5th week	6th week	No "Turbulent Phase" Observed
80	1	10	20	24	5	2	18

TABLE 6—*Relationship Between the Intensity of the "Turbulent Phase" and Final Degree of Improvement*

"Turbulent Phase"		Therapeutic Results — Improvement		
		None	Moderate	Marked
None	18	11	7	0
Mild	7	2	5	0
Moderate	43	2	38	3
Marked	12	0	7	5
Total	80	15 (18.75%)	57 (71.25%)	8 (10%)

From Table 6 it is shown that of the 18 patients who showed no "turbulent phase," 61% (11 patients) failed to respond favorably. 39% (7 patients) responded with moderate improvement and none improved markedly.

On the other hand, among the 62 patients who went through a "turbulent phase" from mild to marked degree, only 6.4% failed; 80.5% responded with a moderate degree of

improvement and 13.1% showed marked improvement. Comparing the data of Table 6 from each group, it would appear that the "turbulent phase" has a definite prognostic relationship to the therapeutic results in reserpine therapy of acute, as well as chronic, psychoses.

During the "turbulent phase," the patient's psychosis appears to be reactivated. He is over-talkative and frequently incoherent; with intensification of his hallucinations and/or delusions. Some of these patients, during this stage of therapy, will occasionally display aggressive behavior. This is associated with a release phenomenon during the early part of highdose therapy on the hypothalamic centers. During the "turbulent phase," the patient rids himself of some of the repressed and deeply buried material and by doing so, the psychic tension is greatly reduced. The "turbulent phase" lasts from 7 to 14 days. With the gradual decrease of the overt psychotic symptoms, the patient appears more relaxed; his speech becomes more coherent and relevant and occasionally during this period, material of psychodynamic importance can be elicited, which at times for years remained hidden and unknown.

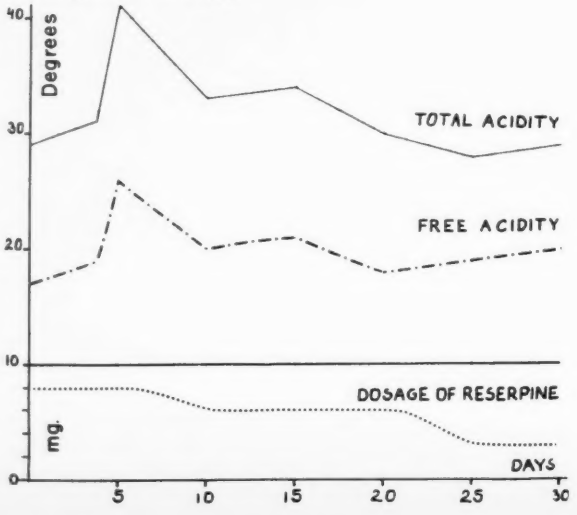
In general, it is believed that the reserpine effect is exerted via alterations of the autonomic mechanism of the hypothalamic region. Studies of Cannon, Ranson[4,23] and more recently those of Magoun,[14,15] established that emotional responses are mediated through the hypothalamic centers and the reticular formation; and the inhibition of these responses is normally cortical inhibition. Clinical studies indicate that the pharmacodynamic action of reserpine is complex and probably involves enzymatic processes of the central nervous system.

Recent studies of Shore, et al.[24] on serotonin and norepinephrine as antagonistic chemical regulators of the autonomic nervous system and the relation to the pharmacodynamic effects of reserpine, regardless of how critical we may be, clearly indicate the possible relation of reserpine to the enzymatic metabolism of amino acids in the central nervous system. The question of the role of serotonin under normal conditions is not yet fully clarified. Woolley[30] suggests a functional relationship to the oligodendroglia. Marrazzi and Hart[16] consider serotonin as a humoral inhibitor of the brain, while Brodie[1] suggests, "that serotonin has a role in the central representation of the parasympathetic nervous system like that of acetylcholine in peripheral synaptic transmission." Brodie's experimental studies show that reserpine strongly decreases the capacity of cells to store serotonin. The liberated serotonin is metabolized by the action of the monoamine oxidase. While in response to large dosage of reserpine, the brain cells may be depleted of serotonin, the amine is still continuously forming in the body by enzymatic activity, so that the rate of synthesis and destruction is kept in balance.

Several patients during the first few weeks of reserpine therapy complained of heart burn. In view of this we selected five cases and studied the stomach content acidity for a period of 30 days. We measured the total and free acidity of the gastric juice and found it increased during the period of high dose therapy. As the therapy continued with the subsiding cholinergic symptoms, the acidity of the gastric juice gradually returned to normal.

In animal experiments it also was shown that in response to reserpine, serotonin is liberated from other body depots, such as the intestinal mucosa and the platelets. This possibly may explain the increased motility

CHART 1—*Demonstration of Changes of the Total and Free Acidity of the Stomach Content During the First 30 Days of Reserpine Therapy*



of the G.I. tract and a moderate increase of acidity of the stomach content during the early stage of high dose reserpine therapy, as we were able to observe in follow-up studies on 5 patients, during the first weeks of reserpine therapy.

The question arises whether such temporary increase of the stomach acidity is due to sudden depletion of serotonin in the stomach mucosa, whether this is due to an inhibitory effect on the conversion of histamine into inactive acetylhistamine, or due to a transient stimulatory effect on the histidase.

From a clinical point of view and for simplicity, the effects of reserpine can be classified into three general groups, as observed in clinical studies on a large number of patients:

(a) somatic effects such as Parkinsonism, cholinergic effect, changes of blood pressure, pulse rate, body temperature and respiration.

(b) psychosomatic effects such as "turbulent phase" with its reactivation of overt psychotic manifestations and increased motoricity, frequently observed bulimia with an uninhibited craving for food, and the increased motility of the G.I. tract with increased stomach acidity.

(c) psychic effects such as decreased psychic tension, decrease of anxiety and the ameliorating effect on the overt psychotic symptoms, the rarely occurring, but highly aggravating states of depression, and occasionally observed inhibition on libidinal drives.

We realize that in some of the signs of the reserpine effect, it is difficult to put a clear demarcation line. On the other hand, the above classification is clinically helpful—as it will be shown—for comparative evaluation of the pharmacodynamics with another compound or combination of therapeutic substances.

In a number of cases on reserpine in repeated studies over a period of time, we observed a slight decrease of blood sugar levels. In separate studies with rescinnamine and deserpidine, the drop of blood sugar was more pronounced and sustained over the entire period of treatment.

The decrease of blood pressure is normotensives in clinically negligible and does not exceed 10 mm Hg (systolic) even during high dose therapy. Except in two cases, the changes in pulse rate and respiratory rate were not significant. Similarly, the decrease in body temperature did not exceed 1° F.

TABLE 7—*Commonly Occurring Side Effects of Reserpine in Group B*

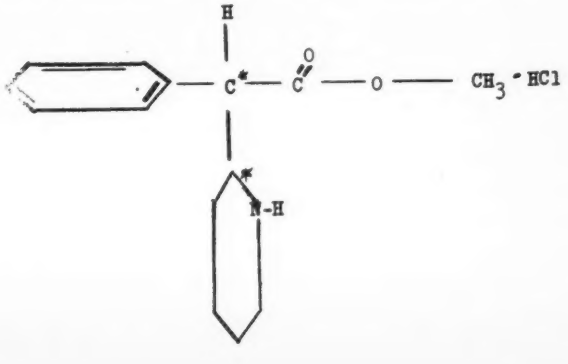
	Parkinsonism	Mucosal Congestion	Drop of Blood Sugar	Bulimia	Depressive States
None	3	8	2	12	37
Mild	27	32	67	22	23
Moderate	38	30	8	31	17
Marked	12	10	3*	15	3

*These three patients were over the age of 60 with slightly increased blood sugar levels prior to treatment.

A 5 to 15% drop in blood sugar level is mild, 15 to 20% moderate and 20 to 40% marked.

The increasing—at times complete—withdrawal and seclusiveness accompanied by more or less pronounced interest in any kind of activity as seen in chronic schizophrenics, and which further promotes regression, constituted an objective of vigorous therapeutic efforts from the very early beginning of chemotherapies.

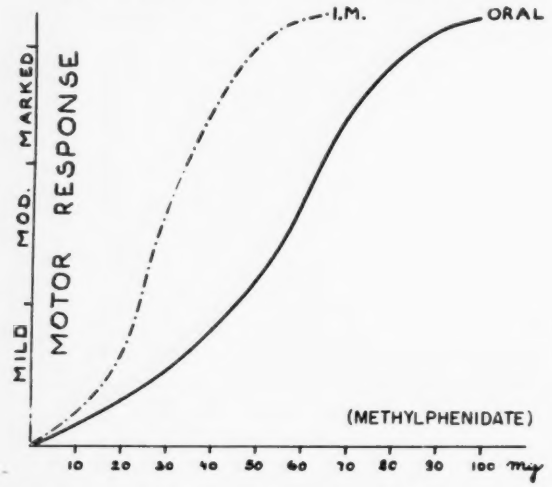
Several years ago Panizzion[20,21] demonstrated in animal experiments with piperidin acetic acid esters that these compounds have a simultaneous, proportional and balanced stimulatory effect on the psyche and motoricity. Methyl α-phenyl-2-piperidineacetate hydrochloride (Ritalin, methylphenidate hydrochloride), a water soluble substance, proved to have such balanced pharmacodynamic properties. Having two centers of asymmetry (marked with stars), there are accordingly two racemates which greatly differ in effectiveness. The pharmacodynamically active form is the meso-compound.



Structural formula of methyl α-phenyl-2-piperidineacetate hydrochloride (Ritalin, methylphenidate hydrochloride), centers of asymmetry marked:

In experimental animals and man, methylphenidate proved to be of very low toxicity. It appears, similar to reserpine, that effectiveness of methylphenidate as a central stimulant as well as its effect on motoricity increases with the degree of differentiation of the central nervous system, i.e., rats, cats and mice show a lesser responsiveness than do monkeys and men. From animal experiments it appears that in animals with lower differentiation of higher centers there is a somewhat predominant effect on motoricity as compared to animals with higher differentiation of the central nervous system. In animals, coordinated but markedly increased motility occurs in response to phenidylate, lasting several hours and then subsiding leaving signs of fatigue. An increase of dosage in relatively small amounts was followed by much more pronounced restlessness and a stage of excitement. Similar observations were made in man, with the difference that the rapid increase of motoricity in relation to the dosage of methylphenidate appeared only after exceeding a certain amount (approximately 50 mg. daily total), and the relationship follows an exponential curve.

CHART 2—*Demonstration of the Increase on Motoricity in Relation to the Total Daily Dosage of Methylphenidate*



In our study with methylphenidate on 40 chronic psychotic patients (Group A), we observed that motoricity was slight at a dosage range of 10 to 40 mg., however, an increase of the dosage above 40 mg. produced, in the majority of cases, restlessness and excitement. Dosages above 60 mg. were accompanied by more pronounced excitement and agitation in most patients, and approximately 50% of the cases showed marked anorexia. Several patients, mostly schizophrenics, had to be discontinued in view of marked agitation and anorexia with a loss of body weight of as much as 20 lbs. within three to five weeks of medication. The increased motor response explains why the agitated type of depression is a contraindication to methylphenidate therapy. The chronic, regressed schizophrenic patients, mainly the catatonic type, are a continuous feeding problem and some of them on methylphenidate showed an outspoken resistiveness to food, resulting in rapid loss of weight. While during the "turbulent phase" with reserpine, an increase of the dosage is indicated; in motor restlessness due to methylphenidate, increase in dosage is contraindicated and only aggravates the condition.

Changes in blood pressure, respiratory rate, body temperature and pulse rate in response to methylphenidate were of no clinical significance. The increase in pulse rate average 12/min. In a few cases we observed an increased motility of the G.I. tract with moderate diarrhea. This occurred only during the first two weeks of therapy; was transient and could be easily controlled by giving 10 to 15 gtts. of Tincture of Opii b.i.d. with good results.

In a group of 100 chronic psychotic patients, on combined treatment with reserpine and methylphenidate (Group C), we were able to observe certain antagonistic pharmacodynamic effects which proved the combination of these substances to be of greater therapeutic value than either of these drugs alone. This was even more evident in the chronic, markedly withdrawn and seclusive schizophrenic patient than in any other case. In combined therapy the overall clinical results were superior to either individual therapy with reserpine or methylphenidate. This appears to be due to the ability of each of these compounds to block, in part, undesirable properties of each without interfering with the other.

In addition to the previously discussed properties of these substances, it should be noted that various derivatives of piperidine are known to exert also a moderate to strong anticholinergic effect. This is necessary for the evaluation of the pharmacodynamic relationship of these two substances. Only in a very few cases, on combined therapy, did we observe congestion of the nasal mucosa and swelling of the eyelids and even then, to a mild degree only. In the majority of cases, the patients on combined therapy showed no evidence of abnormal appetite. In patients on methylphenidate, anorexia was observed and on reserpine bulimia was noted.

In a comparative study on two cases with hypertension (one case with B.P. 210/100 mm Hg prior to therapy, the other case with B.P. 170/95 mm Hg) we observed that methylphenidate does not inhibit the hypotensive effects of reserpine. The inhibition or abolition of the "turbulent phase" as observed in combined reserpine-methylphenidate therapy does not influence the therapeutic results.

Several patients in this group who failed to show favorable response to other chemotherapeutic agents, including methylphenidate, showed improvement to various degrees in response to combined reserpine-methylphenidate therapy. Over the past few years, in our observation of several hundred chronic schizophrenic patients, it was noted that frequently a patient will fail to respond to a certain chemotherapeutic agent or combination, or show only slight improvement, while he may favorably respond to another therapeutic agent or combination. In view of our limited knowledge about the complex biochemical processes, mainly under pathological conditions, there is no explanation for it at the present time and most likely it will be the biochemist and the neuropathologist who may, in the future, give the clinician a clue as to a better application of various chemotherapeutic agents according to clinical diagnosis. At the present time, the clinician's choice of a particular drug or combination of drugs for the treatment of chronic schizophrenics is one of trial and error.

In animal experiments with methylphenidate on dosages close to toxic levels, several observers described clonic twitchings or convulsions.[17] Neither in patients with high methylphenidate dosages (100 mg.), nor in the combined therapy group did we notice clonic twitchings or a single case of convulsions.

Marpurgo and others[18] report the usefulness of methylphenidate administration in post-anesthetic states. In view of the distinct cortical stimulatory effect of this substance in a number of clinical observations, it was noticed that a single I.M. injection of 20 to 30 mg. of methylphenidate markedly hastens the wakening process of the patient from anesthesia, associated with a subjective feeling of well being. He reports that the patient usually within minutes after methylphenidate administration is able to sit up—is fully wakened and cooperative to routine procedures. This, obviously, is decreasing the dangers during postanesthetic states in surgical cases.

Methylphenidate is known to rapidly reduce depressive barbiturate effect. In our observation of 5 cases who had high dosages of barbiturates over a prolonged period of time, the unpleasant side effects were eliminated by injection of 20 mg. of methylphenidate or 10 mg. given orally t.i.d. In four cases of sodium amytal administration in high dosage for an interview, we were able to terminate, at any time, the effect of this drug within a few minutes by a single injection of 20 mg. of methylphenidate. Five minutes after the injection, the patients were fully wakened, offered no complaints and a general feeling of well being was noticed.

Clinical Evaluation

While methylphenidate is of a definite therapeutic value in certain depressive states, its usefulness for the treatment of chronic, regressed and markedly withdrawn schizophrenics, in our observation is questionable —at least in comparison to other presently used chemotherapeutics.

While Ferguson[6] in a group of over 100 chronic cases reports dramatic improvement to methylphenidate, Natenshon[19] even refrains from administration of the drug to borderline psychotic patients. Meier[17] reports good results with methylphenidate in treatment of depressive states, except the agi-

TABLE 8—*Comparison of Common Side Effects with Reserpine, Methylphenidate and Combination of Reserpine and Methylphenidate*

(Expressed in Relative Percentage)

	Reserpine			Methylphenidate			Reserpine & Methylphenidate		
NO. OF PATIENTS	80			40			100		
Response	None	Mild to Moderate	Marked	None	Mild to Moderate	Marked	None	Mild to Moderate	Marked
"Turbulent Phase"	22.5	62.5	15	100	0	0	59	41	0
Increased Motoricity	62.5	37.5	0	15	55	30	45	55	0
Allergic Phenomena	10	77.5	12.5	100	0	0	81	19	0
Parkinsonism	3.75	75.25	21	100	0	0	72	28	0
Bulimia	22.5	58.75	18.75	100	0	0	100	0	0
Anorexia	97.5	2.5	0	12.5	67.5	20	89	11	0
Drop of Blood Pressure	21	75.25	3.75	80	20	0	65	31	4
Tachycardia	2.5	95	2.5	25	75	0	42	54	4
Depressive States	46.25	50	3.75	100	0	0	97	3	0
Hyporeflexia	75	25	0	100	0	0	94	6	0
Hyperreflexia	100	0	0	37.5	62.5	0	88	12	0

tated form of depression; while with schizophrenics, mainly the paranoid type, the therapeutic results were reported less favorable. According to Geller,[8] even among depressed patients, a careful selection of cases is necessary, and, true manic depressive and involutional psychoses should be excluded from methylphenidate therapy.

In chronic, regressed and withdrawn schizophrenics, usually with a history of hospitalization for many years, the administration of methylphenidate alone is of limited therapeutic value. One has to realize the fact that in a chronic schizophrenic patient, his marked seclusiveness, withdrawal and a more or less pronounced lack of interest in any kind of activity is not a result of a depression, but a rather logical sequence of a pronounced break with reality. Participation in everyday activities, interest in the surroundings and in current events, all are part of reality; the reality from which the schizophrenic escapes and for which he substitutes a world of phantasies and dreams. Therefore, it is to be expected that a substance with the pharmacodynamic properties of methylphenidate, in spite of its effectiveness as a central stimulant, can hardly change the basic condition, but a limited degree of increased alertness and a slight improvement of the patient's mental condition can be achieved.

Before giving a comparative analysis of the therapeutic results in our three groups, i.e. the methylphenidate group (A), the reserpine group (B) and the combined reserpine-methylphenidate group (C), it is necessary to discuss the criteria applied. Unfortunately, there is no uniform criterion for the evaluation of the degree of improvement in chronic psychotic patients. It frequently varies from one observer to another and this factor explains the occasional discrepancy in the evaluation of chemotherapies in general. In order to demonstrate what is implied here, let us consider a chronic, stuporous, regressed, schizophrenic, who has been hospitalized for many years. He is out of contact, idle, not accessible to occupational therapy, even on a low level, and only passively cooperative to routine ward procedures. Now, after intensive chemotherapy, this patient starts to show more interest in his surroundings, pays more attention to his personal appearance and finally begins to participate in some form of occupational therapy. One day he starts to talk but his speech is irrelevant and incoherent and his judgment remains impaired. In all fairness, some improvement is evident and no doubt, after many years of frustrating attempts with other forms of therapy, one is easily impressed and tempted to classify such case as "markedly improved." This is, in part, true. Yet, in order to avoid overdramatization, we feel that more rigid criteria should

be applied. Therefore, we consider a patient as "markedly improved" when his mental condition shows such a degree of improvement that he can safely be considered for release from the hospital, and under proper supervision and guidance as well as rehabilitation, he can be expected to adjust on the outside. We fully realize that a chronic schizophrenic, being hospitalized for many years—regardless of how high the degree of improvement may be—will show some residual symptoms.

Another important factor is the question of rehabilitation. The importance of a practical and efficient rehabilitation program becomes even more important if we realize that, in addition to his mental handicap, the patient, after being isolated in a hospital for ten or more years, is released one day to live again in the outside world. So often a patient makes the best attempt to find some place in the society and tries to become a useful member. The question remains as to what extent is the society willing to accept a patient who spent many years in a mental hospital? To what extent is society genuinely willing to lend a guiding hand and have an open mind to understand his shortcomings?

The authors had the opportunity on numerous occasions, to discuss this question with colleagues, a relative of the patient and interest laymen. Frequently the opinion expressed is that this problem is entirely the responsibility of the state. This may be true with some limitations, while on the other hand, the public at large should realize that it is also the responsibility of each citizen. This responsibility is not a financial one alone, but also a willingness to understand and accept the patient with all his limitations. Lack of assuming this responsibility by the community is a contributing factor to the relapse of some patients.

We classify a patient as "moderately improved" when his mental condition shows definite signs of improvement, but not to such a degree that he could be considered for release from the hospital.

Finally, as "therapeutic failures," we consider cases where even after a prolonged period of treatment no essential improvement occurs.

In Group A, of the 40 patients on methylphenidate therapy over a period of 6 to 9 months and, after repeated individual adjustment of the dose, only 3 patients showed marked improvement. Four schizophrenic cases had to be discontinued; 2, due to marked anorexia and excessive loss of weight (over 20 lbs.), within seven weeks and the other 2 because of marked agitation associated with destructive behavior—however, if the dosage of methylphenidate was reduced, the increased motoricity of motor excitement diminished. Except in the 2 patients who had no previous history of agitation or destructive behavior, the reduction of methylphenidate to 10 mg. b.i.d. failed to produce an improvement.

The majority of patients who responded with moderate improvement showed an increased interest in their surroundings as well as personal appearance and began to participate in an occupational therapy program, but their psychotic symptomatology showed little improvement. To illustrate this, we will briefly discuss the case of a 36 year old male schizophrenic patient with a history of hospitalization for over 10 years. He is a patient with mixture of catatonic and paranoid symptoms.

Patient K.P. for the past seven years was in a stage of complete withdrawal, out of contact and idle. Only by observing his behavior on the ward and from his mannerism one was able to conclude that this patient occasionally was actively hallucinating. Any attempt to engage him in some form of occupational therapy completely failed. During the first years of hospitalization this patient had convulsive and insulin coma therapy without any lasting improvement. Also patient had frequent episodes of disturbed and assaultive behavior, and as time progressed, he lost his aggressive drives completely.

During the first three weeks of methylphenidate therapy, the only change observed was increased motoricity and anorexia to a moderate degree. Occasionally he became markedly resistive to feeding. At the end of the eighth week, the original dosage was reduced from 60 mg. to 30 mg. orally o.d. and he began to verbalize, first incoherently,

then with improvement until fairly good contact was established. The motor restlessness subsided and his appetite improved. This patient started to show increasing alertness and interest in various activities and soon became an active member of an occupational therapy group. While he never painted before, he now had completed several oil paintings with a surprisingly good technique. From the motives, colors and composition he prefers, one can clearly see a great deal of his psychotic symptomatology projected into his paintings.

The patient more readily talks about his hallucinatory experiences and some delusional material, which for years remained hidden, could now be elicited. This patient definitely improved, but in view of his mental condition he could not be classified as markedly improved. This case was selected as a typical one to show what we classify as "moderately improved." In view of still persistent overt psychotic symptoms, he could certainly not be considered for release from the hospital.

TABLE 9—*Therapeutic Results in Group A (Methylphenidate) Compared to Diagnostic Classification*

Diagnosis	No. of Cases	Improvement: None	Moderate	Marked
Dementia Praecox:				
Catatonic	12	6	5	1
Hebephrenic	8	3	5	0
Paranoid	10	6	4	1
Mixed	9	3	5	1
Involutional Psychosis, Melancholia	1	0	0	1
Total	40	18 (45%)	19 (47.5%)	3 (7.5%)

Considering the comprehensive reports on the therapeutic values of reserpine in the treatment of various psychiatric disorders, we will omit a detailed discussion and, only for comparison, give the tabulation of the results in our group of 80 chronic psychotic patients.

Group C with 100 chronic patients selected for combined reserpine-methylphenidate therapy, included some 51% of cases who previously had other forms of chemotherapy, including methylphenidate, without essential improvement. Some of the cases selected had shown moderate improvement, but soon after the treatment was discontinued, they began to relapse rapidly. From our observation, owing to the specific pharmacodynamic properties of these two substances and their pharmacodynamic relationship in antagonistic sense, the combined therapy with reserpine and methylphenidate proved to be far superior to either of these drugs alone, and possibly as effective, if not more so, than the combination of reserpine and chlorpromazine.

TABLE 10—*Therapeutic Results in Group B (Reserpine) as Compared to Diagnostic Classification*

Diagnosis	No. of Cases	Improvement: None	Moderate	Marked
Dementia Praecox:				
Catatonic	30	3	24	3
Hebephrenic	12	3	8	1
Paranoid	20	5	14	1
Mixed	10	2	6	2
Other Types (Childhood Schizophr.)	4	1	3	0
Psychosis with Cerebral Arterioscler.	4	1	2	1
Total	80	15 (18.75%)	57 (71.25%)	8 (10%)

Some of these patients who failed to respond to other forms of chemotherapy, showed moderate improvement in response to combined reserpine methylphenidate treatment. In addition to the therapeutic value of this combined chemotherapy, it has the advantage that the unpleasant and undesirable side effects, as observed with either of these drugs, can be eliminated or greatly reduced. Proper adjustment of the dosage of each drug will inhibit the side effects which may predominate.

Reviewing the 84 chronic schizophrenic patients in this group, we notice that some 17.5% failed to respond favorably; 70.9% showed moderate improvement and 11.6% responded with marked improvement to combined chemotherapy with reserpine and methylphenidate. These results are comparable to data obtained from large scale sur-

TABLE 11—*Therapeutic Results in Group C (Reserpine-Methylphenidate) Compared to Diagnostic Classification*

Diagnosis	No. of Cases	Improvement: None	Moderate	Marked
Dementia Praecox:				
Catatonic	22	4	14	4
Hebephrenic	30	5	24	1
Paranoid	10	4	5	1
Mixed	20	2	15	3
Childhood Schizophrenia	2	0	1	1
Psychosis with Mental Deficiency	6	1	3	2
Organic Psychosis	4	1	3	0
Psychosis with Epilepsy	3	0	3	0
Involutional Psychosis	2	0	1	1
Manic Depressive, Depressive	1	0	1	0
Total	100	17 (17%)	170 (70%)	13 (13%)

TABLE 12—*Therapeutic Results in Group C in Relation to the Duration of Hospitalization*

Duration of Hospitalization	No. of Cases	Improvement: None	Moderate	Marked
3 to 5 years	36	1	27	8
5 to 10 years	40	6	30	4
10 to 15 years	24	10	13	1
Total	100	17	70	13

veys as to the therapeutic results in the treatment of chronic schizophrenics with various other forms of combined chemotherapy.

The therapeutic results observed here and in previous studies[13,28,29] in the treatment of outspoken chronic cases, show a definite relation to the duration of the illness primarily, and to some extent, to the degree of deterioration. When we refer to chronic schizophrenic patients, we mean just that and nothing else, i.e. patients with a history of hospitalization for many years and with definite signs of regression and deterioration. Occasionally, some authors in their reports on chemotherapies, use the term "chronically disturbed patients" which may or may not refer to chronic cases, inasmuch as some patients during the acute stage of the illness may be "chronically disturbed" and therefore, such terminology does not clearly indicate the chronicity of the condition. On the other hand, it is a well known fact that many of the chronic and regressed schizophrenic patients do not display disturbed behavior.

As mentioned previously, this group included 51 patients who, during the past three years, had received other forms of chemotherapy without showing any essential improvement, and those who responded with slight improvement, when medication was discontinued, relapsed rapidly. Of these patients 13 failed to respond, 33 showed moderate improvement and 5 patients responded with marked improvement in response to combined reserpine-methylphenidate. It is not intended to claim that this form of combined chemotherapy is outstandingly superior to other forms of combination in the treatment of outspoken chronic psychotic patients, while it definitely gives better therapeutic results than reserpine, chlorpromazine or methylphenidate when used alone. It, however, confirms an observation that frequently one and the same patient may fail to respond to one type of chemotherapeutic agent but when switched to another he may improve in varying degrees.

Among the four cases of organic psychoses, two were general paretics with marked delusions and two were arteriosclerotics with hypertension. The arteriosclerotics, both over the age of 65, responded better to treatment than did the paretics. During a period of observation (over 6 months) we noticed that the hypotensive effect of reserpine was not essentially inhibited by methylphenidate. Both patients tolerated the drugs well without any serious side effects. Within a few weeks after the therapy was instituted these patients became more cooperative to routine ward procedures, appeared more relaxed and showed a general feeling of well being. As the therapy progressed they were less preoccupied with hypochondriacal ideas and began to show an increased interest in various activities. As could be expected from the underlying pathology, certain symptoms such as impairment of memory, decreased

concentration power, etc., showed very little improvement, if at all.

Among the 6 cases diagnosed as psychosis with mental deficiency, we obtained better therapeutic results with the combination of reserpine and methylphenidate than with any other type of chemotherapy. Our experience confirms Carter's observations[3] with this type of patient treated with reserpine and methylphenidate. In general, the superimposed psychosis responded to this form of therapy and the psychotic symptoms usually subsided within 6 to 8 weeks of treatment. Logically the fate and therapy of these patients depends on the degree of their mental defect. Patients in this group who showed marked improvement were released into the custody of their families or transferred to an institution for mentally defectives for training and rehabilitation. The one case of a mentally defective who did not show any essential improvement, was an imbecile with an I.Q. of approximately 25 and functioning on a very low level.

The patients diagnosed as psychoses with epilepsy were long time epileptics with signs of epileptic deterioration, impulsive assaultive behavior and with occasional hallucinatory experiences and paranoid trends. In response to combined reserpine-methylphenidate therapy all three cases showed improvement. The side effects of Dilantin and Sodium Luminal were eliminated in one case and in two cases reduced to negligible minimum. There was a noticeable alertness and an increased interest of these patients in their surroundings as well as personal appearance. While the hallucinations subsided relatively soon after the patient was put on medication, the paranoid trends were much less influenced by therapy. The effectiveness of anticonvulsive drugs was not inhibited. On the contrary, one of the patients who, in spite of high doses of anti-convulsive medication (Sodium Dilantin—1.5 grains and Sodium Luminal—1.5 grains b.i.d.) had several grand mal seizures within a 24 hour period every 5 to 6 weeks. Shortly after he was started on reserpine-methylphenidate, the entire pattern of seizures changed. The markedly increased tension and aggressive behavior, which preceeded his episodes of seizures, subsided after 3 weeks of therapy. He required smaller amounts of anti-convulsive drugs (Sodium Dilantin—1.5 grains and Sodium Luminal—1 grain o.d.) to control the seizures. The seizure-free intervals increased noticeably, and, at the time of his release from the hospital, he had been free of seizures for over 5 months.

It should be noted that relapses are more frequent in this type of patient, and actually, all 3 cases began to relapse within a period of 4 to 8 weeks after the treatment had been discontinued.

The 2 cases of childhood schizophrenia, being of some interest, will be discussed briefly. The 1 patient classified as moderately improved is a case of a 13 year old boy with a history of illness for over 6 years. This patient was markedly deteriorated, actively hallucinating, entirely out of contact and had frequent episodes of highly disturbed and destructive behavior. Electroconvulsive and insulin subcoma therapies bring about no essential improvement. In response to combined therap ywith reserpine and methylphenidate his condition improved after 5 months. The patient appears more alert and interested in his surroundings; no episodes of disturbed behavior were noted during the past 3 months of observation and, only occasionally, was he observed responding to hallucinatory experiences. While he still is in rather poor contact, he will listen attentively when spoken to, and follows instructions. This patient, who for many years was completely idle, is now participating in occupational therapy, but on a low level.

The second case, classified as markedly improved, is a 15 year old boy with a history of illness for over 6 years and who has been hospitalized for the past 3 years. During the first year of his illness he had intensive psychotherapy on an ambulatory basis and when his condition deteriorated, he was hospitalized in a private institution where he received electroconvulsive therapy, without any lasting improvement. While a patient here he received insulin subcoma therapy, subsequently followed by combined reserpine and chlorpromazine therapy. After 6 months of chemotherapy, his condition showed moderate improvement and, soon after he was taken off medication, he relapsed rapidly.

When selected for combined reserpine-methylphenidate therapy, this patient was extremely tense and restless, his speech was rambling; he expressed ideas of reference and delusions of sexual and religious content. Marked inappropriateness of affect was noticed; he was markedly withdrawn and idle. After 5 months of combined reserpine and methylphenidate therapy, this boy's condition showed much improvement. His overt psychotic manifestations subsided completely; his speech became coherent and relevant. In psychotherapeutic session, on a supportive level, he began to verbalize readily and revealed some highly traumatic material which was unknown for years. Several of such incidents were confirmed by investigation of the home and school environment. He is actively participating in an occupational therapy program and attends school where he is reported to be making good progress.

TABLE 13—*A Comparison of the Therapeutic Results in All Three Groups A, B and C.*
(Expressed in Relative Percentage)

GROUPS	No. of Cases	Improvement: None	Moderate	Marked
A (Methylphenidate)	40	45	47.5	7.5
B (Reserpine)	80	18.75	71.25	10
C (Reserpine-Methylphenidate)	100	17	70	13

In our observation therapeutic results with methylphenidate alone in the treatment of chronic and deteriorated schizophrenic patients were not as satisfactory as when this drug is given in combination with reserpine.

Concluding from our observations, we feel that the combined form of chemotherapy with reserpine and methylphenidate has definite advantages which enrich our therapeutic possibilities. While the treatment of these chronic cases is still a great challenge, there is no doubt that progress has been made. The utilization of chemotherapies in the treatment of acute as well as chronic mental disorders is still in the stage of development, but during the few years of existence they have greatly influenced the trend of research and therapy in psychiatry. Regardless of how critical we may be, the fact remains that even in chronic cases, after any other form of therapy has failed, estimated from an evaluation on a larger scale[2,6,7,12,13,28,29] an average of 50 to 60% of cases show moderate improvement in response to chemotherapy, some 10 to 15% respond with marked improvement and all of these cases just a few years ago were prognostically considered entirely hopeless.

Summary

In a comparative evaluation of therapeutic results with reserpine, methylphenidate and a combination of reserpine and methylphenidate, in a total of 220 chronic psychotic patients, we observed that the best therapeutic results were obtained with the combined form of chemotherapy. The 100 patients selected for combined therapy with reserpine and methylphenidate, included 84 chronic schizophrenic patients with a history of hospitalization for many years, and of this group, 51 cases previously had other forms of chemotherapy without favorable results. From this group (C), 17% failed to improve, 70% showed moderate improvement and 13% responded with marked improvement. In the group of 40 patients (A) on methylphenidate alone, 45% failed, 47.5% showed moderate improvement and 7.5% responded with marked improvement. Increased motoricity, up to motor excitement and anorexia, are complications observed with methylphenidate.

It appears from our observations in man, which has been confirmed by animal experiments, that the effect of methylphenidate is not a linear one, but follows an exponential curve. The optimal therapeutic dosage of methylphenidate with minimum side effects, is between 40 to 60 mg. daily, given orally or parenterally. It appears that in certain depressive states, except the agitated depression, methylphenidate is beneficial.

Another advantage of the combined therapy is the fact, that due to the pharmacodynamic properties of methylphenidate and reserpine, in combination, the undesirable and disturbing side effects of either of these drugs can be eliminated, or markedly reduced. Even in prolonged treatment, no

adverse side effects were observed. It also appears that this form of combined chemotherapy has a somewhat wider range of effectiveness in the treatment of chronic psychoses, inasmuch as some favorable therapeutic results were obtained in a group of patients with psychoses associated with mental deficiency and cases of epileptic deterioration. The combination of reserpine and methylphenidate is well tolerated, even in prolonged use, by patients in the older age group with psychoses due to cerebral arteriosclerosis with hypertension, with the advantage that methylphenidate does not essentially inhibit the hypotensive action of reserpine.

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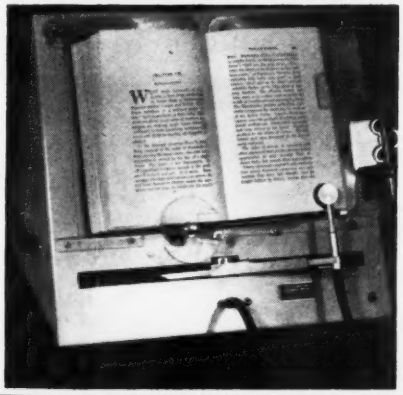

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